UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

DATE

EPA-CASAC-12-XXX

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Integrated Science Assessment for Lead (Second External Review Draft – February 2012)*

Dear Administrator Jackson:

The Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel met on April 10 - 11, 2012, to peer review the EPA's *Integrated Science Assessment for Lead (Second External Review Draft – February 2012)*, hereafter referred to as the Second Draft ISA. The CASAC's consensus responses to the agency's charge questions and the individual review comments from the CASAC Lead Review Panel are enclosed. The CASAC's key points are highlighted below.

The CASAC commends EPA for substantial revisions to the first draft ISA based upon its prior advice (December 2011). Nevertheless, the CASAC has further recommendations for improving the document and recommends that EPA develop a third draft of the ISA and provide it to the CASAC for a review focused on the key changes called for in this letter.

Overarching Comment

Much of the discussion throughout the document is still largely encyclopedic, where individual papers on specific topics are summarized rather than assessed in an integrative manner. Additional integrative synthesis in discussions throughout the document will improve readability.

Preamble, Preface, Executive Summary, and Integrative Summary

The organizational structure of the Second Draft ISA has been enhanced by the addition of a Preamble containing the discussion on the causal framework and by the inclusion of an Executive Summary as

Chapter 1. However, the document still fails to consistently and transparently apply the causal framework to the analysis of the health effects of lead (Pb). The CASAC previously recommended that a thorough appraisal of the strengths and limitations of the epidemiological data be performed on the First Draft ISA and finds that this appraisal has not yet been adequately performed. As per prior CASAC recommendations, the causal determination analysis requires a substantial revision that (1) focuses on specific health endpoints as opposed to organ system effects, and (2) assesses the weight of the evidence for causation critically evaluating the data and systematically applying the causation criteria set forth in the Preamble.

Source to Concentration

The addition of new material to Chapter 3 is an improvement, but there are still problems that need to be addressed. There are many mistakes and issues with the interpretation of the literature, especially in Section 3.5. Adding an integrative synthesis, along with moving much of the detail of the discussion of the studies to an appropriate appendix, will improve the readability of the chapter. Although the discussion of Pb sampling methods in this chapter is improved, the larger issue of the the importance of sampling Pb over a broad range of particle sizes is still not addressed. This omission points to the need for better linkage between Chapters 3 and 4. More information on the role(s) of different Pb particle sizes in terms of human exposure and uptake is needed.

Exposure, Toxicokinetics and Biomarkers

The additions and edits to Chapter 4 are generally responsive to the comments provided by the CASAC on the First Draft ISA. These changes provide a more comprehensive overview of current modeling approaches and available data that are relevant to understanding how air-related exposure can contribute to total Pb exposure. However, the chapter should be improved by:

- Further synthesizing the presented information and data, as well as discussing their implications on the overall exposure assessment or understanding of relationships between exposure and biomarkers of effect;
- Providing table or figure summaries that convey information about uncertainty in the empirical data and model-based estimates of blood Pb / air Pb slope factors. This information should include demonstration of how the range of estimates translates into corresponding changes in the distribution of blood Pb and specifically addressing implications of errors associated with estimates of particle size distributions from historical total suspended particulates (TSP) measurements; and
- Adding a discussion of the implications of the alternative mathematical approaches to fitting blood Pb / air Pb relationships, focusing on the uncertainty in describing the relationship at low air Pb levels.
- Offering a critical assessment of the estimates of the blood Pb / air Pb slope factors that are most appropriate and useful for risk assessment.

Integrated Health Effects of Lead

In general, the revisions made to Chapter 5 addressed several issues identified in the CASAC's review of the First Draft ISA. These revisions include improved integration of the toxicologic and epidemiologic literature in terms of relevant outcomes and exposures, as well as acknowledgement that contemporary blood Pb levels (especially in adults and older children) may not directly account for observed health effects (due to the likely contribution of previously higher or longer term exposures). For childhood IQ, adult nervous system effects, blood pressure, and other cardiovascular outcomes, discussion of the evidence associating these outcomes with Pb, including analyses of consistency (or lack thereof) across the literature, confounding, and study design issues were improved. However, for many of the remaining health measures, a number of important concerns identified in the CASAC's review of the First Draft ISA were not addressed, including:

- Inadequate critical assessment of each study reviewed to determine the strength of the observed associations (e.g., analyses of the potential for confounding, bias, or study design limitations to explain apparent Pb effects were incomplete);
- Lack of transparency, balance, and consistency regarding causal determination;
- Incomplete application of causal determination criteria outlined in the ISA's preamble; and
- Lack of clarity in the description and conceptualization of outcomes (particularly behavioral outcomes).

Although the compelling evidence associating Pb exposure with childhood IQ decrements and adult cardiovascular outcomes (e.g., blood pressure) is well documented in this chapter, the main consequence of the above limitations is likely mis-specification of the weight of evidence supporting causal associations of low-level Pb exposures with other health endpoints, including childhood behavior and adult renal function.

Potentially At-Risk Populations

The expanded discussion and revisions made to the First Draft ISA better capture the intricacies associated with "at-risk" populations. The reorganization of the chapter into related factors also makes it more cohesive and better integrated. The revised Chapter 6 adequately defines some factors as having limited evidence based on the strength of available evidence. However, the extent to which these risk factors actually modify the magnitude of the impacts of Pb exposure is not adequately discussed.

Ecological Effects of Lead

Although new information has been added to Chapter 7, it is not summarized and integrated into a meaningful synthesis and little technical evaluation of extant data is provided. Detailed data should be provided in an appendix and summarized in tables in the text of the chapter. The CASAC also recommends the following: consistent expression of exposure dose throughout the chapter; considering survival, growth, and reproduction as the most relevant endpoints; discussing sub-organismal responses

in the context of secondary responses; and clarifying whether the causal determinations are based on air deposition of Pb or laboratory exposures.

EPA Presentation on Lead Air Sampling

During the meeting, the EPA made a presentation on the development of a new Pb air sampler. The CASAC had previously, on numerous occasions, made the recommendation to replace the high-volume (Hi-Vol) total suspended particulates (TSP) air sampler and is encouraged by and supportive of the development of a new Pb air sampler. As the development of the sampler progresses, the CASAC recommends that the EPA seek out advice and review from the CASAC's Air Monitoring and Methods Subcommittee (AMMS).

The CASAC appreciates the opportunity to provide advice on the ISA and looks forward to reviewing the third draft of the ISA.

Sincerely,

Dr. Jonathan M. Samet, Chair
Clean Air Scientific Advisory Committee

Dr. H. Christopher Frey, Chair
CASAC Lead Review Panel

Enclosures

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names or commercial products does not constitute a recommendation for use. The CASAC reports are posted on the EPA website at: http://www.epa.gov/casac.

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Consensus Responses to Charge Questions on EPA's Integrated Science Assessment for Lead (Second External Review Draft – February 2012)

Preface, Preamble, Chapters 1 (Executive Summary) and 2 (Integrative Summary)

The CASAC panel offered a number of recommendations to enhance the organization and presentation of the evidence in the ISA. An Executive Summary has been prepared and is included as Chapter 1. As part of the development of the Executive Summary and restructuring of the integrative overview chapter, Chapter 1 materials have been revised and moved, specifically: (a) the more general sections on the development of the ISA and the causality framework are being placed in a Preamble that can support all ISAs; (b) the introductory sections specific to this ISA describing the ISA development and scope are placed at the beginning of Chapter 2; and (c) sections on legislative background and history of previous reviews are contained in a Preface in the front matter of the ISA. The intent was to bring the integrative overview discussion to the front of the document, thus making it more accessible to the reader, and to streamline the ISA organization.

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy or presentation of these summary sections and the conclusions therein.

In addition, please comment the extent to which the discussion of the health effects evidence in Chapters 1 and 2 reflects the revisions to Chapter 5, which were designed to characterize the weight of the evidence for specific endpoints as well as the strengths and limitations of the studies.

The organizational structure of the 2nd External Review Draft of the Integrated Science Assessment for Lead (2nd Draft ISA) has been enhanced by movement of the general description of the ISA development process and the causation framework to a Preamble, and by the inclusion of an Executive Summary as Chapter 1.

<u>Preface</u>

The subsection within the Preface entitled "History of the NAAQS for Pb" should be improved by adding a discussion of aspects of the pre-promulgation history, notably the contribution of public interest lawsuits and court decisions to the initiation of the National Ambient Air Quality Standard (NAAQS) process. It will also benefit from a discussion of lead (Pb) being a multimedia pollutant, which is unlike other criteria pollutants. Hence, although regulating Pb air concentrations reduces total Pb exposure, other sources and pathways can still affect Pb intake.

Chapter 1 (Executive Summary)

The revisions made to Chapter 1 (moving material to the Preface and Preamble) and making it an Executive Summary are appropriate. Some further improvements that should be made to this chapter include: mentioning that the main pathway of Pb intake for most people is Pb ingested from dietary sources; adding a statement to Section 1.3.1 that there is variability in the reversibility of health effects across systems; and stating that Pb occurs naturally at a range of background levels in soil which are not toxic to soil-dwelling biota that have evolved in the presence of Pb.

Chapter 2 (Integrative Summary)

Chapter 2 includes a summary of the other chapters of the ISA. The CASAC's comments and recommendations for the respective chapters are detailed in the consensus responses and should also be reflected in the summaries in Chapter 2.

A major conclusion of the CASAC's review of the 1st Draft ISA was that the document failed to consistently and transparently apply EPA's established causal framework to the analysis of the health effects of Pb. A thorough appraisal of the strengths and limitations of the epidemiological data was recommended, and it was suggested that summary tables of the relevant literature include a column that specifically highlighted these features. These same major concerns and shortcomings continue to apply to the causal determination analysis that appears in the Executive Summary, Chapter 2, and Chapter 5 of the 2nd Draft ISA. As per prior CASAC recommendations, the causal determination analysis will benefit from a substantial revision that (1) focuses on specific health endpoints as opposed to organ system effects, and (2) assesses the weight of the evidence for causation after systematically and critically evaluating the data for:

- Strength of study designs (in accordance with the standard epidemiological hierarchy: prospective cohort study, nested case control, case control, cross-sectional, etc.);
- Consistency in terms of the nature and strength of the observed associations;
- The extent to which associations arising from chance, bias, or confounding have been ruled out with reasonable confidence;
- Demonstration of a dose-response relationship, focusing particularly on the presence of effects at current or former environmental Pb doses (i.e. blood Pb levels < 25 µg/dL);
- Biological plausibility of effects at low doses demonstrated by findings from toxicological investigations; and
- Findings that might identify the cumulative Pb dose or temporal pattern of blood Pb concentrations at which the causal impacts may occur.

As discussed further below in the consensus response on Chapter 5 and the individual comments of several panel members, particular concerns exist regarding the causation analysis of behavioral effects in children, and renal effects in children and adults. With respect to behavioral effects in children, the analysis summarized in the Executive Summary and Chapter 2 will benefit from a critical appraisal that acknowledges: (1) inconsistency in findings observed within the published literature (particularly

notable if older, high quality, prospective studies omitted from the current ISA are considered); and (2) the potential for observed associations to have been subject to confounding or bias as a consequence of the limited extent to which many studies have been able to adjust for parental behavior or psychopathology. Behavioral outcomes in children should be distinguished from effects on cognitive function, and the authors should reconsider the frequent tendency for the narrative to refer to the impact of Pb on both of these endpoints as if they occur jointly or with equal causal weight.

With respect to renal effects, the narrative should offer a more balanced assessment in which causal inference is tempered by:

- Inconsistency in the literature (underscored by the existence of studies that observed no significant relationship or a relationship in which increasing blood Pb levels were associated with improved renal function);
- The potential contribution of reverse causation; and
- The paucity of toxicological studies that identify a nephrotoxic mode of action of Pb on the kidney at the low doses in which a reciprocal relationship between blood Pb and glomerular filtration rate (GFR) may have been observed.

The uncertainty that characterizes the relationship between Pb exposure and asthma and allergy should be acknowledged, as only one or two epidemiological studies of each of these endpoints have been discussed in the document, and those are subject to methodological limitations.

The terminology utilized in the ISA to characterize causal relationships between Pb and various health endpoints often merits revision. For example, in several instances the narrative states "the weight of the evidence supports associations" (e.g., see Table 2-10 section on neurobehavioral effects; page 1-7, line 12; and many places in Chapter 5). This phraseology is ambiguous with respect to causal assessment, because an epidemiological "association", however strong, is by itself insufficient to establish causation, particularly if bias and confounding cannot be ruled out with reasonable confidence.

The new subsection in Chapter 2 on "Public Health Significance" (section 2.9.1) is a positive addition to the document. This chapter appropriately notes that the magnitude of change observed in certain parameters in epidemiological studies (e.g., decrements in IQ or increases in blood pressure) may be of limited clinical impact in any one individual, yet nonetheless signify a substantial public health impact on the population as a whole. It would be prudent for this section to focus on the impacts of Pb on cognitive functions in children, and blood pressure and cardiovascular disease in adults, and to curtail or eliminate discussion of other endpoints (such as behavior, immune dysfunction, and renal dysfunction) for which the effect of Pb at low dose is less well established. With respect to the discussion of the public health impact of Pb on IQ in children, it should be noted and discussed that the validity of Figure 2-1 is predicated on the incremental dose response of Pb on IQ being of similar magnitude in children with low and high intelligence. The sentence on page 2-54 line 20 should be rephrased to note that there is "no level of Pb exposure shown to be without deleterious effect" rather than refer to "no safe level of exposure". A consideration of the level of exposure to a hazardous substance that is considered "safe" involves risk management issues that are beyond the intended scope of the subsection.

Chapter 3 – Source to Concentration

Revisions made to Chapter 3 in response to CASAC comments include elaboration of changes to the National Emissions Inventory between the 2006 Pb AQCD and the ISA (Section 3.2), discussion of the limitations of the current total suspended particulate federal reference method sampler and available alternatives (Section 3.4.1), removal of questionable data presented for particle size Pb comparisons (Section 3.5.3), addition of a background Pb section (Section 3.5.5), and supplementation of studies to elucidate the relationship between air Pb and Pb in soil (Section 3.6.1).

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. Is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

This chapter is improved from the prior version with substantial new material, but there are still problems that need to be addressed. There are many mistakes and issues with interpretation of the literature, especially in Section 3.5. Much of the discussion is still largely encyclopedic, where individual papers are summarized, rather than providing an integrated assessment of the science. Adding an integrative synthesis, along with moving much of the detail to an appropriate appendix, will improve the readability of the chapter (especially Section 3.5). In addition to the information on the largest Pb source categories, it would be useful to add a list of the largest individual Pb emission sources, along with contextual information comparing population exposures from large individual sources, such as smelters, to exposures from large source categories, such as piston aircraft. Additionally, EPA should review the recent Aucott and Caldarelli (2012) study on Pb in wheel weights. Chapters 3 and 4 have some common elements that will benefit from more direct cross-chapter linkage between exposures and Pb-air measurements. One example is wood smoke (3.2.2.5 and 4.1.3.1).

The expanded description of the Pb Total Suspended Particulates (TSP) Federal Reference Method (FRM) and related Pb sampling methods in Section 3.4.1 has substantial new and helpful content in response to comments on the 1st Draft ISA, especially on the current FRM high-volume (HiVol) sampling method. A limited discussion on the possibilities of and need for a better alternative FRM has been added, but still ends with "...there is a continued need to assess the feasibility of a revised TSP sampler design..." without discussing how to move forward towards the promulgation of a revised FRM TSP sampler. Although it may not be within the traditional scope of an ISA, an expanded discussion on the state of the aerosol science supporting possible alternatives to the HiVol TSP FRM would be useful to address the many and long-standing CASAC comments on this topic. EPA should consider addressing what might be acceptable (from an exposure perspective) and practical for sampler performance (e.g., d50 cut size, cut curve shape / sharpness (geometric standard deviation), and wind speed dependence). EPA should discuss whether the measurement of very large airborne particles is meaningful, useful, or desired given the indirect nature of the dominant exposure pathways. EPA should also discuss whether a modest decrease in design value concentrations from a robust larger particle FRM sampler would be important, considering the relatively large uncertainty in all other aspects of the relationship between air Pb concentrations and health outcomes. This topic is closely related to exposure

and dose. The Integrative Summary states that "the Pb-TSP indicator was retained in 2008 in recognition of the role of all PM sizes in ambient air Pb exposures", but relatively little information is presented (in Chapter 4 or elsewhere) on what the role(s) of different Pb particle sizes are in terms of human exposure and uptake.

In Section 3.5.3, Size Distribution of Lead-Bearing PM, EPA should consider further broadening the scope of this topic beyond studies in the peer-reviewed literature; all data on Pb size above 10 µm are useful given the limited literature on this topic. The summary of Air Quality System (AQS) data in Table 3A-13 (ambient air Pb particle size information) in the appendix of the first draft should be revised (not removed) to include only concurrent, paired samples above the method detection limits (MDLs). Again, improved linkage to Chapter 4 will be helpful; for example, Table 4-3 will benefit from information about the size fractions measured in these studies.

In Section 3.5.4, Lead Concentrations in a Multipollutant Context, use of Spearman rank r alone to describe associations with other pollutants may not be sufficiently informative. EPA should consider also presenting or evaluating Pearson or another parametric r, and should justify what was used. Some filtering of results to those that are meaningful for use in source identification would make the material more accessible.

In Section 3.5.5, Background Pb Concentrations, the issue of how to define "background" should be further discussed. In the first paragraph, the policy relevant background (PRB) is defined as "those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America." This definition contrasts with the more scientific definition of a "natural" background, unaffected by any anthropogenic sources. Both are difficult to assess, but the natural background is probably easier to evaluate. In any event, the section does not come to a conclusion on what the background levels might be; the section is comprised of several paragraphs explaining why it is difficult to estimate PRB levels. It should be possible to bracket a range for background airborne, soil, and aquatic Pb concentrations.

Chapter 4 – Exposure, Toxicokinetics and Biomarkers

The exposure section of Chapter 4 includes additional discussion of the relationship between airborne Pb-particle size distribution and exposure by inhalation and ingestion (e.g., hand-to-mouth). Cross-referencing to Chapter 3 further emphasizes measurement errors and uncertainties that may affect exposure assessment for air Pb. A new section on exposure assessment methodologies was added that includes discussion of exposure representation within the IEUBK model and exposure modeling techniques.

The revised toxicokinetics section of Chapter 4 expands discussion on the effects of both past and current Pb exposure on blood Pb levels. Studies that followed blood Pb levels in individuals following cessation of high Pb exposure occupations and in children over the first several years of life were added. The section on bone Pb measurement was expanded. Air to blood slopes were reevaluated across

the range of air Ph concentrations available in a given study with an emphasis on the central tendency of air Pb concentrations in each study.
With consideration of these revisions, please comment on the accuracy of the interpretation of the science. Are uncertainties and limitations of relevant data, methodologies and approaches adequately discussed? Where appropriate, please provide specific recommendations to refine the scientific interpretation and/or improve the representation of the science.

The additions and edits to Chapter 4 are generally responsive to the comments provided by the CASAC on the 1st Draft ISA. These changes provide a more comprehensive overview of current modeling approaches and available study data that are relevant to understanding how air-related exposure can contribute to total Pb exposure. However, there are several areas where the chapter can be improved.

Additional synthesis and summary of information is needed on the following:

- Section 4.1 – Section 4.1.3.3 (Dietary Lead Exposure) – The information is factual, but the reader will benefit from more interpretation, context, and summary. The chapter should include additional discussion to explain the importance and impact of the reviewed data to the ISA. This recommendation can be generalized to all chapters of the ISA document – EPA should review each section and determine if, in addition to summarizing the information/data available, the implications of this information also are conveyed.
- Section 4.1.1, p. 4-6 – The additional paragraph is helpful at presenting quantitative estimates of percent contribution of air Pb to blood Pb. A table that summarizes this information should be included which distinguishes between estimates based on modeling (e.g., IEUBK) and empirical studies. Text should be added to synthesize/summarize this information with specific focus on the importance of changes in these percent contribution estimates over time, or as a function of the low-end versus high-end blood Pb levels.
- A section should be added that relates estimates of blood Pb / air Pb slopes to the original goals of the ISA as presented in the Integrated Review Plan, which called for an uncertainty analysis that provides a foundation to review the NAAQS. For example, the ISA can demonstrate how a particular slope factor translates into a corresponding change in blood Pb at the geometric mean (GM) and 95th percentile of the distribution, assuming a lognormal distribution with geometric standard deviation (GSD) of 1.6 (which is adopted in the IEUBK model).

Additional discussion and perspectives on the relevance of information as presented is needed:

- Chapter 4 leaves the impression that from a multipathway exposure perspective, direct inhalation of air Pb is generally a relatively minor contributor to total dose compared to soil/dust ingestion, diet, water ingestion and other routes of exposure (although some exceptions are noted, such as populations living in the vicinity of an airport). This impression may raise questions regarding the interpretation of the blood Pb / air Pb slopes, or the potential for a reduction in NAAQS to have a meaningful effect on blood Pb. Chapter 3 provides a more explicit discussion of the correspondence between air Pb and multiple exposure media (beyond air itself). There needs to be a better linkage between Pb air concentration and exposure in Chapters 3 and 4.

- The discussion in Section 4.2.1, p. 4-30, lines 24-28 needs to be expanded to include the concept that time-integrated blood Pb reflects an aggregation of the biological processes that includes both recent Pb bioavailability/absorption as well as inputs from soft tissue and bone.
- The simulations in Figures 4-8, 4-9, and 4-11 are very informative and help to illustrate the temporal profile of Pb in blood, bone, and overall body burden. The text (p. 4-63) indicates that the simulations represent an exposure scenario in which a child experiences "a constant Pb intake (from age 2-5) via ingestion…followed by an abrupt decline in intake." Additional details regarding the exposure/dose will be useful - specifically what constant Pb intake was administered, and when intake was abruptly reduced – was the intake set at zero or some non-zero baseline? Further clarification on the relevance/interpretation of the time averaging would be useful because it is unclear how the reduction in variance attributable to the averaging can be related to the experimental data. The EPA should consider removing the time-weighted average blood Pb panel.
- Figure 4-22 is a very helpful addition to demonstrate the various slopes, particularly to emphasize the differences in the model selection (e.g., log-log, log-linear). The shapes of the response curves are very divergent at low air concentrations. Given that the focus of the NAAQS is at the low end of the air Pb range presented, EPA should (1) comment on the challenge of estimating the low-end of the curves (i.e., < 0.2 $\mu g/m^3$) from data collected, and (2) comment specifically on the magnitude of difference in estimates and representativeness of the statistical models applied to empirical data. EPA should conduct an independent analysis of the underlying studies and determine if a common model can be used to describe all the datasets. Then, the EPA should relate the analysis back to estimates of expected change in blood Pb associated with change in NAAQS (see third bullet under additional synthesis above).
- The ISA presents a range of blood Pb / air Pb slope factors without pinpointing a subset of estimates that may be more relevant to the objectives of the REA. To the extent that the EPA has already identified a "best estimate" of a slope factor, or a range of best estimates that are most appropriate and useful for risk assessment, this information should be included in the ISA, accompanied by a discussion of the rationale that supports the selection.
- The EPA should discuss the importance of errors associated with estimates of particle size distributions from historical Pb TSP measurements. How does this uncertainty likely contribute to (1) estimates of air Pb / blood Pb slopes; (2) estimates of predicted blood Pb from epidemiological data; and (3) corresponding uncertainty in predicted change in blood Pb associated with reduction in air Pb (see third bullet under additional synthesis above).
- Section 4.1.1 presents the conceptual model for a multi-pathway assessment. Page 4-6 (lines 8 to 34) discusses the relevance of particle size distributions for inhalation and soil/dust ingestion exposure pathways. The first sentence (line 8) states that particle size of Pb-PM is relevant to transport through various media leading to exposure. This sentence should be restated or the introduction should be expanded to emphasize that different ranges of particle sizes are relevant to different exposure pathways.
- The historical perspective on the change in Pb sources over time associated with the change in blood Pb remains somewhat biased towards the phase-down of gasoline Pb (e.g., Section 3.7.1;

Section 4.4.1, p. 4-78, introductory paragraph). It should also emphasize the role of reductions in emissions in the vicinity of point sources as presented subsequently (e.g., pp. 4-84 to 4-86).

The following contradictions need to be addressed:

- The text on clearance rates for blood Pb (e.g., 4-62) suggests that the rate of change may be slow following cessation of exposure, such that blood Pb will remain elevated years after exposure ends. Yet, the narrative discussion at the top of page 4-67, and the model simulations in Figure 4-11 (ICRP modeling) suggest exactly the opposite – a rapid decline in blood Pb following cessation. EPA should provide more description regarding model assumptions (e.g., how baseline exposure was factored in), and comment on whether this relationship may differ for higher blood Pb that corresponds with adult occupational exposure. If available, the document should discuss literature that provides empirical observations for the change in blood Pb following cessation of exposure that resulted in moderate elevations (e.g., blood Pb in the 10 to 25 µg/dL range) for various time durations. There is concern regarding the external validity of the simulation in Figure 4-11, in which blood Pb was shown to decline to baseline levels within months of termination of exposure that had resulted in a blood Pb concentration more than 300% above baseline for 25 years.
- Pages 4-39 (line 23) and 4-120 (line 22) report that 1% of the Pb body burden is in blood, whereas page 4-49 (line 12) reports that 5% of the Pb body burden is in blood.

Chapter 5 - Integrated Health Effects of Lead

In Chapter 5, the integration/synthesis of evidence between epidemiologic and toxicological studies and across related outcomes has been expanded throughout the text and in summaries of individual endpoints. In the summary and causal determination sections, we have described more explicitly the weight of evidence for each endpoint within a broad outcome category and specified the particular endpoints that contribute most heavily to the determination of causality. We have noted, where applicable, uncertainties regarding the specific Pb exposure periods, levels, frequency and duration that contributed to epidemiologic observations and included additional details and discussion of study limitations.

Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.

For childhood IQ, adult nervous system effects, blood pressure, and other cardiovascular outcomes, discussion of the evidence, including analyses of consistency (or lack thereof) across the literature, confounding, and study design issues were improved. However, for most of the remaining health measures, a number of concerns identified in the CASAC's review of the 1st Draft ISA remain unaddressed.

These unaddressed concerns include:

- Incomplete critical assessment of each study reviewed to determine the strength of the observed associations. The review did not systematically address the adequacy with which epidemiologic studies have ruled out the potential influence of bias, confounding, or other study design limitations on findings and the extent to which multiple high quality studies have reached consistent and replicate findings. This critical approach would mean not necessarily accepting study authors' conclusions for a number of studies but the critical approach was done infrequently, if at all. There was rarely a distinction made between associations observed in cross-sectional versus longitudinal studies despite important differences in inferences possible from these two study types. Differential weighting of cross-sectional and longitudinal studies should be done but generally was not. Most, if not all, of the epidemiology studies of Pb and immune function were cross-sectional but the implications of the cross-sectional design (such as reverse causality) were not acknowledged.
- Lack of transparency and consistency regarding causal determination. A *balanced* analysis of the strengths and weaknesses of the literature (see the previous bullet above), consistency (or lack thereof) across the literature, and causal determination criteria outlined in this ISA's Preamble were not applied consistently across the chapter's sections. For some outcomes, null studies or studies that do not support the conclusions were not reviewed or were reviewed in a cursory manner. For example, the null associations of Pb with child neurodevelopment noted after adjustment for Home Observation for Measurement of the Environment (HOME) score and other covariates in the Ernhart et al. (1987, 1988, 1999) prospective studies were briefly described in the text but absent from relevant figures (Figure 5-2), tables (Tables 5-3, 5-4), and conclusions. Similarly, two prospective studies of Pb and attention-related measures that did not show consistent findings were not included in reviews of the Pb-behavior literature (Wasserman et al., 2001; Canfield et al., 2003). As a final example, a recent review contending that the available published literature does not support the conclusion that low level Pb exposure causes renal dysfunction (Evans and Elinder, 2011) was not cited in the chapter. There might be good reasons for excluding or down-weighting these studies but, absent any rationale for doing so, it appears that non-confirming studies may have been given insufficient attention. As a consequence, EPA's causation criteria pertaining to "consistency" and "replication" by multiple high quality studies may not have been adequately addressed with respect to a number of endpoints.
- For some outcomes, the approach to causal determination needs to be revisited to consistently include the adequacy of study design (see the previous two bullets above), toxicologic support, and biological plausibility. The phrase "the weight of evidence supports the association" is used throughout the chapter primarily to describe consistently observed associations but the use of this phrase does not address the requisite elements of a "weight-of-evidence" causal determination. In the epidemiology literature, consistently observed associations, however strong, are not sufficient to establish causation particularly if non-causal explanations for the associations (e.g., residual confounding or bias) cannot be ruled out with reasonable confidence. An example is the possibility that confounding by maternal (parental) psychopathology, particularly an attention deficit hyperactivity disorder (ADHD) diagnosis or subclinical deficits in attention, may explain apparent associations of Pb with ADHD. This is a major limitation in studies of ADHD in

particular, where family history may reflect both heredity and parenting behaviors contributory to ADHD risk. For studies of Pb and ADHD or ADHD-related behavior that were reviewed, credible information about maternal (parental) diagnosis was not available.

- Example consequences of the above limitations in the weight-of-evidence analysis include: (1) the weight of evidence relating Pb with childhood cognition versus behavior is not the same but the text implies it is; (2) this draft addresses some previous concerns and is more measured than the 1st Draft ISA in its presentation of renal effects but still does not adequately address major concerns with the Pb-renal epidemiologic literature. These include the potential for reverse causation, inconsistencies and uncertainties among studies, and absence of a plausible mechanism for renal effects at low blood Pb levels.
- For some health measures, the weight-of-evidence analysis was undermined by lack of clarity in the description and conceptualization of outcomes, particularly behavioral outcomes. For example, behavioral check lists or formal psychometric tests of attention should not be equated with a clinical diagnosis of ADHD. The evidence associating Pb with ADHD is limited (essentially all cross-sectional studies) whereas there is more substantial support for an association of Pb with inattention. This important distinction is unclear in the document. In general, behavioral outcomes were considered superficially without careful characterization of differences among different study endpoints. Based on the review of the chapter, it was sometimes difficult to determine the strength of Pb's associations with child behavior because distinct outcome measures were often blurred or intermixed. Comparable behavioral assessments are necessary for meaningful comparison of findings across human studies. If not done already, consulting with experts in psychometric assessment (for both clinical diagnosis and research purposes) and experts in animal behavioral testing might help promote a more rigorous approach to interpreting and drawing comparisons among the complex and diverse behavioral measures in the literature. For example, the assessment of the human behavioral literature should include a clearer distinction between outcomes defined by behavior check lists and those defined by clinical diagnosis. Similarly, a more robust approach to identifying homologies between animal and human behavioral test measures is needed.

Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiologic studies, in particular: the increased emphasis on toxicological findings most relevant to Pb-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Pb-associated health effects. Has the coherence of findings among related endpoints been sufficiently described? Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.

The revised Chapter 5 includes better integration of the epidemiology and toxicology literature with, in most cases, a clearer focus on comparing (or acknowledging) homologous tests and exposure routes in animal and human studies, an improved discussion of the relevance of mode of action studies to human health effects, and a more explicit description of the relevance of exposure levels used in the toxicology literature to human exposure and/or modes of action. However, in some cases, homologies between animal and human tasks were over-extended or ambiguous. For example, in the section on nervous

system effects, homologies between the Morris Water Maze and Cambridge Neuropsychological Test Automated Battery (CANTAB) were over-extended. Furthermore, the CANTAB is not a specific test so stipulation of the relevant test in CANTAB is needed in any comparison with animal tests. Similarly, in animal models where "overall FI rate" is designated "a hyperactive behavior" (see page 5-92), it is unclear how this characterization might be homologous to ADHD-like behaviors in children which are largely related to issues of distractibility and impulsivity, rather than movement. Also, for some outcomes (e.g., some immune effects), the most robust associations with Pb are seen in the toxicology, but not the epidemiology literature. This distinction and its implications are not made clear. With respect to renal endpoints, the fact that the experimental animal studies summarized in Chapter 5 utilized Pb doses (e.g. in the tens to hundreds ppm of Pb in water or diet) that were many orders of magnitude higher than recent community environmental exposures, and yielded blood Pb concentrations in the animals considerably higher than recent general population levels merits clear acknowledgement in section 5.5.6 (Summary and Causal Determination).

Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). Are inferences regarding the specific Pb exposure scenarios (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?

The revised chapter is consistent in acknowledging that contemporary blood Pb levels in adults (and older children) may not directly account for observed health effects because of the likely contribution of previously higher or longer term exposures. In this context, the chapter is correct to note uncertainty with respect to the precise Pb dose associated with an outcome. Nevertheless, for the endpoints of blood pressure, hypertension, and cardiovascular mortality, secular trends in blood Pb and bone Pb data would allow the EPA to reasonably conclude that decades of blood Pb concentration in the range of 10-25 μg/dL likely bears a causal relationship with elevated blood pressure and increased cardiovascular mortality in susceptible populations. The epidemiological data support this finding by virtue of consistent findings in multiple high quality studies that have adequately controlled for bias and confounding. In addition, toxicological and clinical data offer evidence of plausible biochemical mechanisms at this level of exposure. In contrast, among studies of children, acknowledging "…uncertainty regarding the frequency, timing, dose…of Pb" associated with an outcome may be appropriate for a number of populations but is less of an issue for studies of most U.S. children growing up in recent times when blood Pb levels have been lower and less variable. Nonetheless, even in certain studies of the relation of blood lead to health effects in children, uncertainty may remain regarding the independent contribution of prenatal exposure.

Some exposure characterizations need refinement. For example, characterizing prenatal or early infancy exposures in humans as "short duration" could be misleading because short duration exposures during critical periods of development (such as prenatally) can have profoundly deleterious, long term consequences.

The document is inconsistent in its approach to exposure timing. For example, critical exposure periods are discussed in detail in the nervous system section but, at least for human data, there is minimal, if any, discussion of this issue for immune system effects.

Lastly, in discussions of non-linear dose-response relationships, the distinction between supralinear and U-shaped dose-response curves is not always clear. Lack of effect at high levels may be observed with U-shaped, but not supralinear, dose-response.

Additional Comments

In addition to the above charge questions, key comments on this revised Chapter 5 include:

- A new section on the public health significance of nervous system effects is informative and adds to the weight of evidence presented. However, this discussion alludes to a figure on page 2-55 that is based on a statistical model rather than observed data. This fact needs to be made clear because, with all models, findings are predicated on assumptions that may or may not be true. Specifically, the figure and related inferences are based on assumptions about both the baseline distribution of population IQ values and expected changes in that distribution associated with Pb exposure.
- In some places, the chapter is difficult to read due to run-on sentences, repeated text, lack of transitional text, and factual errors. In the extreme cases, the intended meaning of some sections of the chapter cannot be deciphered (as an example, see the discussion of the potential for differential survival time to bias Pb's association with Amyotrophic Lateral Sclerosis on page 5-164).

Chapter 6 - Potentially At-Risk Populations

The introduction to Chapter 6 has been revised with expanded discussion to better capture the intricacies associated with characterizing populations potentially at greater risk for Pb-related health effects. Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

In addition, please comment on whether the designation of some factors as having limited evidence adequately reflects the knowledge base considered and strength of evidence available.

In general, the expanded discussion in the revised chapter better captures the intricacies associated with "at-risk" populations. The reorganization of the chapter into related factors also makes it more cohesive and better integrated. The revised chapter adequately defines some factors as having limited evidence based on strength of available evidence.

Some issues still remaining include the extent to which these risk factors actually modify the magnitude of the impacts of Pb exposure. As currently constructed, there is no way to discern which of these risk

factors is most critical and certainly a better understanding of magnitude of the impact would be of assistance for risk assessment and management.

The CASAC has the following recommendations for improving the chapter:

- Given the differences between maternal self-esteem (how was it actually measured) vs. stress imposed in rat models, such a homology should certainly be limited or at least qualified.
- The statement regarding the impact of arsenic on Pb bioavailabity (p. 6-3, lines 33-35) should be re-checked for accuracy because the cited study (Wang and Fowler, 2008) does not support the statement.
- Section 6.3.6 (Race and Ethnicity) and Section 2.9.6.5 do not sufficiently discuss the potential susceptibility of African Americans to Pb possibly arising from factors not mediated by socioeconomic status (SES) or exposure.
- There are statements in Chapter 2 suggesting interactions between Pb and fluoride and co-exposures. There appears to be additional information related to this, and a discussion of Pb and fluoride should be added to Chapter 6, including limitations and uncertainty. The statement on page 2-78, lines 29-31 regarding the influence of fluoridation on Pb in water is not supported by the scientific studies presented elsewhere in the ISA, and it should not be included in its current form.

Chapter 7 - Ecological Effects of Lead

The causal statements for ecological effects discussed in Chapter 7 have been reevaluated as advised by CASAC. There are now separate causal determinations for terrestrial and aquatic biota for each endpoint under consideration. In addition, the chapter now incorporates additional findings from the 2006 Pb AQCD on the effects of Pb on ecosystem receptors, an enhanced discussion of bioavailability and bioaccessibility, and separate discussions of marine and freshwater toxicity in the aquatic ecosystem section.

Please comment on the adequacy of these various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information.

This chapter has been greatly improved by reorganization and the inclusion of additional material. Sections have been clarified with the addition of concise introductions, by reference to previous Air Quality Criteria Documents (AQCDs), and the inclusion of brief summaries of sections, where appropriate. More recent information on Pb exposure, toxicity, and effects to ecological receptors has been included in separate sections for terrestrial, freshwater, and marine ecosystems. Although the revised ISA contains new information presented in an organized manner, the information is not summarized and integrated into a meaningful synthesis and little technical evaluation of extant data is provided. Summary tables listing media-based exposure concentrations (soil, freshwater, marine), nominal or measured, with their respective responses and key abiotic modifying factors (e.g., pH, organic carbon, cation-exchange capacity (soils), water hardness) will help in further organizing the data to facilitate a synthesis. A detailed table should be provided in an appendix (e.g., 2006 Pb AQCD) with a

summary of the most relevant data presented in the ISA to guide the discussion. An initial discussion should include the relevance of responses observed at very high Pb levels that may not be expected in most environmental scenarios. In a similar manner, Pb exposures and effects related to very low levels also should be addressed, especially where Pb levels appear to be below analytical detection limits. Discussion could then conclude with an evaluation of how the ranges of Pb found in various media (see Table 2-1) overlap with experimental concentrations. Although some discussion of bioavailability is provided, integration of this concept into the discussion of observed effects of Pb exposure in different media should be attempted.

Throughout the chapter, the consistent expression of exposure dose will help facilitate comparisons of exposures within and among studies. Exposure doses should be expressed on a mass basis (e.g., mg/kg, mg/L) for all exposures, except for comparisons between or among metals, where exposure should be expressed on a molar basis (e.g., µM). Nominal concentrations and exposures in non-standard media (e.g., hydroponic, agar) should be identified.
The EPA's Office of Water utilizes the endpoints of survival, growth, and reproduction for the development of water quality criteria. Pb that is subject to atmospheric deposition and results in ecological effects would ultimately be present in water, sediments, or soils. Survival, growth, and reproduction should be considered the most relevant endpoints, and sub-organismal responses should be discussed in the context of secondary responses.

The nature of the question that is asked in causal determinations as related to ecological responses needs to be clarified, i.e., What is a "relevant pollutant exposure" (Preamble, page lv)? Are causal determinations related to aerial deposition of Pb or are they only considered in relation to laboratory exposures even though relevance to ecosystems is unclear?

There is a need for consistent linkage of terms for causal determination with chapter 2.

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Appendix A

Compendium of Individual Comments by CASAC Lead Review Panel Members on EPA's Integrated Science Assessment for Lead (Second External Review Draft – February 2012)

Mr. George A. Allen

General Comments

Revisions to Chapter Three generally address the panel's comments on the first ISA draft. Some sections have been reorganized and expanded, and there are several new subsections. Some of the new material, especially in section 3.5, may not been carefully reviewed internally; there are many mistakes and issues with interpretation (or lack thereof) of the literature discussed. Chapters 3 and 4 have some common elements that would benefit from more direct cross-chapter linkage. Chapter 4, section 4.4.1 notes the Miranda dx.doi.org/10.1289/ehp.1003231) 2011 study of blood lead in children living in the vicinity of GA airports. This study's results imply that inhalation may be a major pathway of exposure to GA airport Pb, but there is no discussion of this in section 4.1.3.1, Airborne Lead Exposure.

HERO continues to be useful, especially for material that is not in the published literature.

Specific comments on Chapter 3:

Section 3.2.2.5, "Description of air Pb emissions from wood burning" discusses the contribution of this source to air Pb, primarily from wildfires, as a "potentially uncontrollable source." There is still no meaningful discussion of avoidable Pb exposures from residential space heating woodsmoke; this may be the primary air exposure pathway for "new" Pb in rural or small valley towns where woodsmoke PM concentrations can be high for much of the winter. Chapter four cites one limited study (Molnar, 18 woodsmoke samples) on these exposures with minimal discussion because p=0.06; despite the p-value, this is a notable result given the small sample size.

Section 3.4.1, Ambient Lead Monitoring Techniques, has substantial new content in response to comments on the first draft ISA, especially on the current FRM Hi-Vol TSP sampling method. A limited discussion on the possibilities of and need for a better alternative FRM has been added. While it may not be within the traditional scope of an ISA, an expanded discussion on the state of the (aerosol) science supporting possible alternatives to the Hi-Vol FRM would be useful to address the many and long-standing CASAC comments on this topic. It would be useful to have some discussion here and/or in chapter 4 on an acceptable FRM particle size cut from an exposure perspective; is a "TSP" measurement that has well characterized under-sampling of large particles at higher wind speeds sufficient to assess exposures to Pb in the context of NAAQS-relevant exposure pathways? Is measurement of very large particles meaningful or useful given the indirect nature of the dominant exposure pathways?

Section 3.5, Ambient Air Lead Concentrations, has been substantially expanded and revised in the second draft. Overall the changes are an improvement, but some of the new material needs more careful proofing and editing; this section can be difficult to read and understand at times. There is a tendency to present material but not synthesize it in the larger context of this section or chapter. Sometimes data are presented without noting the sampling method; this is difficult to interpret since measurement of larger particles depends on the sampler. 3.5.1.2, Intra-urban Variability, has several new subsections: near-

roads, airports, and urban-rural that provide additional useful detail. Section 3.5.3, Size Distribution, appears to be a nearly complete re-write of this important topic and would benefit from additional editing to make the information more readily accessible. Section 3.5.4, Multipollutant Context, also has a large amount of new material that needs cleaning up. Section 3.5.5, Background Concentrations, is new; although Pb background is not much of a factor relative to some other NAAQS (ozone for example), this discussion is useful.

Specific comments follow (page, line[s]).

3.3.1.3, 3-27, 15-25. This discussion of maximum height above ground is confusing and doesn't seem to be consistent. One cite has maximum height of 75 um particles as 0.4 m and another has it as 0.05 m. There needs to be a discussion on this wide range of reported or modeled data if the cites are correct.

3-27, 27-32. "long range transport of dust" limited to particles < 10 um. If LRT here is meant in the traditional sense (100s of km or more), 10 um is too large.

3.4.1.1, pg 3-58, table 3-3. The PM10 SSI HiVol FRM should be included here; it is mentioned in the text.

3.4.1.6, pg 3-67, 6-7. Highly time-resolved measurements are also valuable for determining sources. This section should mention the "on-line" Cooper/Pall Xact 620 XRF ambient sampler: http://www.pall.com/main/OEM-Media-Membranes-and-Materials/Product.page?id=54499.

3.4.2.1, GA Airport monitoring. Although the results of the first year of GA airport monitoring won't be available until spring 2013, there will be some useful information available by this fall. There are six GA airports with 2008 NEI emissions over 1.0 tpy; the highest is Deer Valley (Phoenix) at 1.3 tpy. One of the 15 airports in the 1-year pilot study has emissions during the summer similar to Deer Valley's tpy. Nantucket (MA, ACK) has 0.76 tpy according to http://www.epa.gov/ttn/chief/net/2008nei_v1/lead_facility_v1_5_final.xls, with much (more than 2/3?) of this during four summer months. Thus the emissions during the 3-month rolling average form of the Pb NAAQS from mid-June to mid-September are perhaps higher than any other GA airport. It would be useful to have monthly airport activity information to better understand these seasonal emissions patterns at Nantucket.

3.5.1.1, variability, pg 3-79, table 3-6. It may be worth noting that the "highest" values reported here are not stable numbers due to the limited 6th day sampling and the strongly skewed distribution of the data. Same for table 3-8, pg. 3-82.

3.5.3.2, airborne Pb near roadways.

3-99, 30-31: UF, fine and coarse Pb "roughly constant" - makes no sense; units are mg/kg [typo]

3-100, 5: units? Line 22: what size range/cut?

3-101, 4-5: the 1 to 10 um bin concentration should be reported too.
8: NOx reactivity cause of lower R2? NOx in the near-road context is conserved.
11-12: mean is lower than winter/summer concentrations

3.5.3.3, airborne Pb other urban/rural.

3-102, 28-29. PM 1-2.5 is too large for a ~ 1:1 fine/course aerosol.

3-104 fig 3-28: correlation of 1.0 for 3 categories - is this real?

3-105, 1-3: R or rho?

3-107, table 3-10. Most of the reported correlations across sizes are implausible.

3.5.5, background Pb.

3-109, 23-25: sentence makes no sense.

Typos:
3-67 line 16
3-74 line 8
3-76 line 2
3-99 line 22, 28
3-103 line 14-21: awkward, hard to understand; punctuation error? “figures illustrates”

Dr. Herbert Allen

Chapter 7 - Ecological Effects of Lead

This draft of the ISA represents a substantial improvement of the document. Chapter 7 is well-written and comprehensive. The assessments are based on the studies presented and are easily followed.

p. 7-70. L. 6-16. This presents only the inorganic species that are present. To state that these are the forms that are present is not true and is countered elsewhere. In addition to these inorganic forms, lead humate is present in the solid phase and lead fulvate is present in solution.

p. 7-75. L. 5. and p. 7-134. L. 7. "commercially-derived humic acid" is a poor description. If this was Aldrich Humic Acid, state that as this is a widely used material.

p. 7-75. L. 13. µmole is a unit of mass, not of concentration. If this was 1 µmole/liter, write 1 µM. The unit µM means µmolar or µmole/liter. This error occurs in a number of other locations.

p. 7-85. L. 8. 2.9 and 6.6 mg Pb is not in the correct units. The mass of plant tissue considered must be presented. Perhaps this should be mg Pb/ g plant. Likewise, in the next line, the mass of sediment must be indicated. Perhaps this should be 0.3 mg/ g sediment.

p. 7-88. L. 16. The volume of water is not indicated. Perhaps this should be 0.05 µM rather than 0.05 µmole.

p. 7-88. l. 34. Perhaps "rate" should be deleted as time is not a variable.

p. 7-92. L. 8. Report the concentration of Pb not of Pb-nitrate. An example of a good style is p. 7-93. l. 20.

p. 7-92. L. 24-26. This is not clear. Why is the average Pb in sediment given together with the range of values for body burden? Why not provide ranges for both or use mean values for both? Is this whole body?

p. 7-101. L. 18 µmole is a unit of mass, not of concentration.

p. 7-102. L. 8, 14 and 35. mmol is a unit of mass, not of concentration.

p. 7-102. L. 15. µmol is a unit of mass, not of concentration.

p. 7-103. L. 6. mmol is a unit of mass, not of concentration (twice).

p. 7-104. L. 2. Na^{+} not Na^{2+}. Ca^{2+} not Ca^{+}.

p. 7-110. L. 36 and 37. Ca^{2+} not Ca^{+}.

p. 7-110. L. 38 Probably Ca^{2+} not Ca.

p. 7-111. L. 1. Probably Zn^{2+}, Cd^{2+}, Na^{+}, Cl^{-}, Ag^{+}, and Cu^{2+}.

p. 7-111 l. 2 and 4. Probably Ca^{2+} and Na^{+}.

p. 7-111 l. 17 and 23. Ca^{2+} not Ca^{+}.

p. 7-113. L. 8. Were these exposure concentrations analytically verified? These are among the lowest concentrations cited in this chapter and this are of importance in establishing the concentrations that can elicit biological response. 10 nM Pb is approximately 2 µg/L. Low concentrations of Pb are difficult to maintain and, of course, the potential for contamination always exists.

p. 7-114. L. 9. The unit is not expressed clearly, but I take it to be 0.3-0.48 g Pb/ kg wet fish · day. This value is HUGE. Is the unit for Pb mass correct?

p. 7-114. L. 26. The second value in the list should probably be 0.01 rather than 001.

p. 7-115. L. 6. These concentrations are even less than those in p. 7-113. L. 8. On a weight basis they correspond to 0.02 to 0.2 µg Pb/L. That is a concentration below that found in most freshwaters. If goldfish are representative of all fish, the conclusion is that most fish are affected by environmental lead exposure. This is a very serious finding and the results should be very carefully assessed and the discussion should be increased. In the next sentence of the ISA the results of an estrogenicity cell growth assay in the same study are reported. The cited paper indicates that EC_{50} value for lead was 1×10^{-14} M. This is, I believe, the lowest effect concentration reported anywhere in the ISA. It is 4-5 orders-of-magnitude below the effect value in the vitellogenin evaluation. I am greatly concerned about this entire study. To maintain these low concentrations of lead is exceedingly difficult. Normally, I would expect to find that the entire study had been carried out in a Class 100 clean room and would expect to find that the nominal concentrations that are reported in the study had been confirmed analytically, e.g. ICP-MS. The authors point out that result for cadmium chloride was 4 orders-of-magnitude below the value that had been previously reported. This should have raised concern about the results.

p. 7-127. L. 16-22. Because the chemical reactions involved in considering critical load should be expressed with molar units rather than weight units, the difference in critical loads for different metals should also be compared on a molar basis. The atomic weight of Pb is more than 3 times that of Cu, Ni, and Zn. Comparing moles a metal loading at the critical load, the value for lead is approximately a factor of 3 greater than that for the other metals, not an order of magnitude greater.

p. 7-133. L. 20-25. The constancy of Na^{+}, Ca^{2+}, and Mg^{2+} concentrations is true for marine systems that are little influenced by fresh water. However, very important saltwater systems are embayments and

estuaries. Saltwater systems encompass a range of salinities from just above that of freshwater to full strength seawater.

p. 7-152. L. 21-25. This is not what is shown on the next page. Bioaccumulation does primarily occur from uptake of Pb from water via the gills.

p. 7-166 l. 17. Is there a chlorophyll that contains Ca?

Dr. Richard Canfield

In Chapter 5, the integration/synthesis of evidence between epidemiologic and toxicological studies and across related outcomes has been expanded throughout the text and in summaries of individual endpoints. In the summary and causal determination sections, we have described more explicitly the weight of evidence for each endpoint within a broad outcome category and specified the particular endpoints that contribute most heavily to the determination of causality. We have noted, where applicable, uncertainties regarding the specific Pb exposure periods, levels, frequency and duration that contributed to epidemiologic observations and included additional details and discussion of study limitations.

Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.

1. **Interpreting Bayley MDI results**: The Bayley MDI test is nicely introduced (p. 5-65) but could benefit from an explicit statement that although it statistically analogous to IQ, it is not an IQ test and, when administered prior to about age 2 or 3 years, does not consistently correlate with childhood IQ when measured during childhood or later in life. It is somewhat misleading to lump together Bayley test results from 6 months to 3 years because many of the items on the 3 year MDI are quite similar to items that appear on the WPPSI, Stanford-Binet, and other IQ tests when administered to the youngest age groups. Because children change so rapidly during infancy and early childhood, there is not a single item on the 6 month MDI that also appears on the 2 or 3 year MDI. It's still called the MDI, and that is a source of confusion. In reality, there is little agreement on what the MDI measures, especially in the normal range of infant and child developmental outcomes. When the MDI does predict later IQ it is typically a case in which an at-risk sample (e.g., brain infarcts during delivery, vlbw)includes some infants that are severely impaired and some that are normal and then the prediction is really more of a test of whether those groups develop differently or reach different IQ endpoints. If I were to assess the strength of the evidence for causality based on the PbB-MDI literature (not having reviewed it as recently or as comprehensively as was done for this ISA), I would say that MDI data are not inconsistent with the IQ results but that the measure is poorly suited for this purpose and the results are not wholly consistent, yet they do not provide a basis for questioning the results seen with IQ testing at later ages.

2. **Confirmation bias**: The concern about a confirmation bias stems from examples such as the treatment of results from the Cleveland cohort study(Ernhart et al. studies). This is a prospective longitudinal study that gave substantial attention to covariate control, yet found nonsignificant

effects of lead after adjustment. A key concern with the handling of this study is that it could appear that it was considered not important solely because the findings did not agree with the bulk of the research in this area (more so for IQ than for MDI). This impression is greatly amplified by noticing that although the study is briefly described in the text, alongside the other studies, it does not appear in the summary tables and figures in both sections where it is relevant. That is, in section 5.3.2.1 Ernhart et al. studies are absent from figure 5-2 and table 5-3 (p. 5-57 to 5-59). This is also true for the section describing MDI results on p. 5-66 to 5-68 where the Ernhart studies are not included in table 5-4. As a result of these omissions, the figure and tables contain only evidence that supports the conclusions of the document. There might be good reasons for excluding those studies but in the absence of any rationale for giving them no apparent weight in characterizing the strength of support for the conclusions raises the concern that non-confirming studies were, in general, given insufficient attention.

3. **Homology**: In a number of instances the homology asserted to exist between performance of animals in toxicology studies and children in epidemiological studies is at times overstated. For example, the Morris Water Maze task, as typically administered, is a test of spatial navigation or place learning using distal landmarks. However, it can be administered in a simplified form by using local landmarks, and it can be administered such that the location of the platform is different for each testing day. None of these versions can be considered directly homologous to the CANTAB tests used in the Rochester study. On 5-73 the CANTAB is described as "sharing homology" with MWM but on 5-88 it is stated that "The Morris Water Maze is homologous to the spatial memory components of the CANTAB and WISC-R, which test the ability of subjects to recall correctly a sequence of locations." The MWM typically involves only one location and so here the homology is somewhat weak. On 5-100 MWM results are characterized as "These animal observations provided strong coherence with associations in children with homologous tests of spatial memory and rule learning and reversal." And on 5-102 "…tests of learning and memory in animals that are directly homologous to tests conducted in children.." Moreover, the CANTAB tests administered in the Rochester study are part of the working memory and planning battery and is shown to depend heavily on frontal areas. On the other hand, MWM is generally considered a hippocampal task. This would suggest that they are not homologous.
    a. Going deeper into the interpretation of CANTAB, several different tests were given and each measures a somewhat distinct aspect of cognitive function. Thus, the spatial working memory task (SWM) requires the subject to recall which of several boxes had been visited previously on that trial to retrieve the reward. This is most homologous to a radial arm maze task. The spatial span task (SSP) measures something slightly different. It is designed to test the maximum number of locations that can be held in working memory and then recalled to guide behavior (pointing). Because there is essentially no

delay imposed, these are measures of visual-spatial working memory that I would agree "share homology" with

(note also that MWM is a stressful task, which could influence the cognitive and emotional functions measured)

1. **Coherence/relating specific cognitive measures to IQ:** on page 5-55 it is stated that "specific indices of cognitive function are reflected in global measures of intelligence." It's unclear what is being claimed here…correlations between specific tests and IQ are sometimes close to 0…for example some executive function measures aren't well reflected in IQ and in the reviewed study by Canfield et al. using the cantab some measures were associated Pb independent of IQ.

5-118 Decrements in cog function and behavior problems demonstrated within same population is not direct evidence for cognitive underpinnings of behavior problems…have studies looked at assoc between cogn and behavior in the same children???

5-102 and 5-191 and elsewhere…"relatively short durations of lead exposure" are considered to be conception through birth or even into postnatal life. In tox studies short can be 1 hour or 24 hours in cell cultures. The term is misleading in the context of continuous prenatal exposure and should be dropped. On 5-213 (l. 27) frontal lobe and striatum are mentioned but not hippocampus

Interpreting dose-response curves: (p. 5-223 and elsewhere) U-shaped dose-response curves from toxicology studies are clearly different from the supralinear concentration-response curves often seen in epidemiological studies using IQ as the outcome. In the latter case it is always true that more Pb is worse than less Pb, it is just that the adverse effect of a unit of exposure is greater at the lower levels. In the former case there are groups for which a greater Pb dose is associated with less (or no) damage as compared to the larger effects of a lesser dose.

Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiologic studies, in particular: the increased emphasis on toxicological findings most relevant to Pb-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Pb-associated health effects. Has the coherence of findings among related endpoints been sufficiently described? Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.

Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). Are

inferences regarding the specific Pb exposure scenarios (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?

1. Frequent unevenness from paragraph to paragraph and section to section on whether there was both an introductory statement about the health-relevance of an outcome and a summary statement about what the reader should conclude from the review of studies in relation to that outcome. This ranged from often-excellent to nonexistent.
2. "There is uncertainty regarding the frequency, duration, timing, and magnitude of exposure contributing to the blood Pb levels among the adult [adolescent, child] population studied." (2-74) This type of statement is frequently made in the integrative summary in relation to adult and adolescent cross-sectional data. It is also relevant for interpreting results of cross-sectional studies in school-aged children and should be mentioned in chapter 5 Integrated Health Effects.
    a. For example, BPb of 2 at 8-11 years is difficult to interpret regarding threshold or low-level effects because we don't know what the earlier exposures were.

5-214 pub health significance: Might include issue of societal use of cut-off scores on IQ-like tests to qualify for admission to college, grad school, etc. The loss of a few points could have substantial life-long effects on the individual's opportunities, regardless of the absolute magnitude of the difference in ability that is represented by a few point lower IQ score.

5-86 table 5-6 Beaudin et al. and Stangle et al. studies show most prominent effect in error reactivity, which they characterize as an emotional effect. This interpretation should be considered in sections 5.3.3.2 (5-137) and/or 5.3.3.5 (5-145)

Chelation

Recent work in Strupp lab shows that chelation alone results in some cognitive impairment and so interpretation of this literature depends on knowing this.

5-100 Methionine choline supplementation did not reduce brain Pb but did cause improved learning and memory in rats. This could be due to an independent effect of choline supplementation during the early postnatal period. Information about the ages period of choline supplementation should be included in the writeup and a reference to work by Williams and Meck on choline effects in the rat.

5-112 MMSE is a screening test for cognitive impairment and NOT at test of general cognitive function.

There is more diversity to associations between age of BLL and correlation with later outcome than is made clear in the document. For example, in Boston, only 24-mo Pb correlated with 57 mo IQ whereas in Rochester 24-mo lead showed the lowest correlation with 3 and 5 yr IQ.

SES- Good discussion of a complex issue. One instructive comparison could be considered for inclusion…Rochester and Boston included children at near opposite ends of SES and IQ distribution, but had very similar BLL profiles. They also showed very close estimates of effect size and supralinearity of effect curve.

5-151 Differential effects in children and adults…should include mention that affectingapparently different neuropsych processes operating at different ages could also be variation due to different ages of exposure and exposure profiles in the various studies.

Should be some mention of "filedrawer problem" in which some studies fail to be published due to nonsignificant results whereas results significant by chance association would more likely see publication. This is a source of uncertainty.

5-259 5.4.3.3 Heart Rate Variability….need intro on how to interpret the measure, why is it important? Need introduction similar to 5.4.3.2 or 5.4.3.4.

Dr. Deborah Cory-Slechta

Comments on Chapter 5

My comments on Chapter 5 are primarily editorial, with one exception. I am concerned about associating lead with ADHD. All but one of these studies is based on teacher and/or parent report and not a clinical diagnosis, hence the reliability of such a diagnosis is questionable. There is significant support for an association of Pb with attention-related behaviors, and maybe this is the appropriate terminology, unless there is some reference that can show reliability of teacher/parent reports to actual clinical diagnosis.

p. 5-26; lines 16-20; are the increases vs. decreases related to Pb level and perhaps indicative of a non-linear curve?

p.5-27, lines 22-24; again, could it also be indicative of non-linear concentration-effect functions?

p. 5-47, lines 25-27: increased apoptosis of what?

p. 5-55, lines 11-12: I think significant caution needs to be exercised in ascribing Pb exposure to ADHD. Most of the studies cited in support of this are based on parent and or teacher reports and not on an actual clinical diagnosis, which makes them far less credible (albeit teacher reports are likely better than parents).

p. 5-75, Figure 5-5: It would be helpful if the actual names of the tests were used here; they are for some of the studies, but not others, e.g., for Chiodo the table lists 'perseverative errors', but on what test? The specific tests are not listed in Table 5-5 either for many of the studies, just references to e.g., Cantab. It would be particularly useful to somehow incorporate the specific test names (e.g., rule learning and reversal is the IntraExtra Dimensional Shift Set).

p. 5-88 line 4: change mouse to rodent, the test is used with both rats and mice

p. 5-89, line 5-6: again, the name of the specific test being referred to should be included. To cite this as 'components of the Cantab' is confusing as there is not "the Cantab" but a menu of specific tests one can use from Cantab.

p.5-91, line 14: should be two months not two weeks

p. 5-99, lines 4-7. Its not clear why this distinction is being made; for both humans and animals, the subjects assess the ability to complete a task when the 'rules change'. That is the same thing as say 'changes in reinforcement'.

p. 5-114, lines 23-24. Not sure that it is really appropriate to say that the relevance of the plasma Pb fraction is not clear; we know that this is the fraction that delivers Pb to soft tissue. For example, in chelation studies, e.g., Korean workers after CaEDTA, it is the plasma Pb compartment that shows increases in Pb even as blood Pb levels decline and in animal studies that same procedure results in increases in tissue Pb levels, including brain.

p. 5-120, lines 9-20: it would be more appropriate to describe the test as "shift focus to another dimension of the stimulus that defines correct responding (e.g., color to shape)"

pp. 5-128-132. Here again, I repeat the concern about linking Pb to ADHD specifically which is a clinical diagnosis. All but one of the cited studies for this section relies on parent and or teacher reports, which is far less confirmatory. Options include citing this significant limitation, looking at the literature to see how predictive teacher reports of ADHD are relative to clinical diagnosis, or describing these as 'attention-related' deficits.

p. 5-138, lines 16: should change "absence of a fixed schedule of reinforcement" to something like " time interval preceding the availability of reward opportunity".

p. 5-138, line 19: change 'interresponse rates' to 'interresponse times'

p. 5-138, line 27 change 'repeat-acquisition' to either 'repeated acquisition' or 'repeated learning'

p. 5-150, line 9, change "frontal striatum' to 'frontal cortex and striatum'

p. 5-150, line 10, delete space before period after 'density'

p. 5-151, line 6, change 'processed' to 'processes'

p. 5-207, lines 21-25. A reference needs to be added for this description of outcomes.

Comments on Chapter 6

I have no major comments for Chapter 6, the revised version of the draft has addressed my prior comments. The only thing that I think would still be useful is some indication of magnitude of the differences in Pb toxicity that can occur with some of the factors that confer susceptibility or risk. In particular, while polymorphisms can induce differential risk, what is the magnitude of the differences that they are associated with? It would seem that an understanding of the risk associated with such factors would be useful for risk assessment and for the question of whether or not the current methods of ascribing safety factors of 3 or 10, for example, actually accommodate those susceptibilities.

Dr. Cliff Davidson

Preamble and Preface: The revised ISA does a good job of separating material that can support all ISAs and putting this in the Preamble. The Preamble and Preface read well, and contain appropriate material. There are a few editorial comments:

Page xlv, line 19: "animal toxicological studies includes" should be "animal toxicological studies include"

Page xlv, lines 25-26: the word "should" sounds prescriptive and doesn't match the rest of the section. Should be modified.

Page xlvi, lines 22-24: remove "the health effects evidence from" and "evidence" as the last word of the sentence.

Page xlvi, line 24: "first draft ISA" is confusing – should be this "second draft ISA"?

Page xlviii, lines 1-7: First sentence on the page is too long, and in any case it is a run-on sentence. Start new sentence beginning :more generally.."

Page xlix, line 17: "Controlled human exposure studies" at the beginning of the sentence should be "Such controlled studies…"

Page l, lines 4-5: sentence has three negatives in it, difficult to read.
Page l, lines 33-34: "this potential threat to inferential validity" should be "the potential for erroneous inferences"

Page li, lines 34-36: This sentence should be revised as follows: "For example, an individual of low socioeconomic status or with a pre-existing disease may have increased risk of effects related to air pollution exposure; either of these factors may be an effect modifier."

Page lvi, line 6: "Surgeon" is misspelled.

Page lxi, line 9: revise after the semicolon to read: "for example, there is no established change in any lung function measure that represents an adverse effect."

Page lxi, line 14: delete "For example"

Page lxix, line 14: change semicolon to a comma – currently incorrect grammar. "2" should be a superscript.

Chapter 1. Chapter 1, as the Executive Summary, is a brief outline of the full ISA, and incorporates enough background so that the reader will know whether to make the investment in moving on to Chapter 2, which is a much more detailed integrative summary. The chapter reads well and there are only a few very minor edits suggested:

Page 1-5, line 14: sentence has grammatical problems.

Page 1-7, line 2: define AQCD

Page 1-7, line 12: define SES

Page 1-9, line 26: delete comma

Chapter 2. A reader should be able to read this chapter and come away with a good idea of what studies are relevant to the NAAQS for Pb and how they fit together. As an integrative summary, Chapter 2 now accomplishes that. The chapter reads well and contains the requisite information. The problem remaining is to incorporate changes in the later chapters back in Chapter 2 so that it is consistent with these changes. The CASAC suggested a number of changes in Chapters 3 through 7, and those will be summarized in the consensus report. Thus the substantive edits to Chapter 2 will come later.

Page 2-13, lines 24-26: sentence has grammatical problems.

Page 2-24, line 34: “association” should be “associations”.

Page 2-60: the description of Table 2-61 is too brief. Some individuals will read Chapter 2 and never get beyond this chapter. Table 2-61 is important and merits a bit of discussion.

Dr. Philip E. Goodrum

Comments on Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

Chapter 4 describes the multimedia nature of Pb exposure, toxicokinetics of Pb in humans, biomarkers of Pb exposure and body burden, as well as models of the relationship between Pb biomarkers and environmental Pb measurements.

The pre-meeting memorandum to the Pb CASAC Panel notes that the following items were updated in Chapter 4 of this second external draft:

Exposure

- Additional discussion of the relationship between airborne Pb-particle size distribution and exposure by inhalation and ingestion (e.g., hand-to-mouth).
- Further emphasis on measurement errors and uncertainties that may affect exposure assessment for air Pb.
- Addition of new section on exposure assessment methodologies that includes discussion of exposure representation within the IEUBK model and exposure modeling techniques.

Toxicokinetics

- Expanded discussion on the effects of both past and current Pb exposure on blood Pb levels.
- Presentation of additional data from studies that followed blood Pb levels in individuals following cessation of high Pb exposure occupations and in children over the first several years of life.
- Expanded section on bone Pb measurement.
- Reevaluated air-to-blood slopes across the range of air Pb concentrations available in a given study with an emphasis on the central tendency of air Pb concentrations.

Charge to CASAC committee:

Comment on the accuracy of the interpretation of the science:

1. Are uncertainties and limitations of relevant data, methodologies, and approaches adequately discussed?
2. Provide specific recommendations to refine the scientific interpretation and/or improve the representation of the science.

General Comments

The additions and edits to Chapter 4 are generally responsive to the comments provided by CASAC on the first draft of the ISA. These changes provide a more comprehensive overview of current modeling approaches and available study data that are relevant to understanding how air-related exposure can contribute to total Pb exposure.

The ISA presents a well organized and systematic overview of the key elements of exposure assessment for Pb. The addition of cross references to other chapters and references to the 2006 Pb AQCD, guidance documents, and risk assessment literature improves the overall readability. Important concepts that help to describe the role of air-related lead exposure are more clearly introduced. However, the synthesis of this information could be further improved so that the ISA provides a stronger foundation for the review of the NAAQS. An important shortcoming of Chapter 4 is that it does not succinctly address the key questions based on the evidence presented. According to the Integrated Review Plan for NAAQS (November 2011, p. 4-9), the ISA is intended to address the following questions regarding Pb exposure:

- Can air-related pathways be disentangled from water- and soil-related pathways using available data (and modeling approaches)?
- How do new studies inform the assessment of exposure to air-related pathways?

The Summary and Conclusions (Section 4.7) ends by offering the following perspectives (with my paraphrasing):

- Air-lead concentrations are decreasing, but it continues to be challenging to disentangle air-related pathways from other exposure pathways.
- Extensive monitoring data exists and sampling errors contribute to uncertainty in exposure assessment.
- Modeling approaches are available, but errors in measurements and assumptions can propagate through to the model predictions of exposure and blood lead concentrations.

Toxicokinetics information can help us understand the complex relationship between a life history of exposures, biomarkers of exposure, and predicted changes in biomarkers with changes in air lead sources. But without sufficient long-term monitoring data, it is difficult to quantify these relationships for specific populations.

- Air-lead / blood-lead relationships can be established by evaluating specific studies. Variability in study designs and findings introduces uncertainty in extrapolating results to populations on a broader scale.

While this is a thoughtful articulation of the uncertainties of both empirical and modeling approaches to exposure assessment, the document seems to be missing an uncertainty analysis that more directly

informs the science-policy decisions. Given these uncertainties, what specifically can be said regarding the assessment questions noted in the Integrated Review Plan?

Specific Comments and Suggestions

Section 4.1.1 Pathways for Lead Exposure

- p. 4-2. Very good addition of the discussion on the importance of particle size in determining relative contributions of inhalation vs. ingestion. This paragraph helps to set the stage for Figure 4-1 that follows. Further, it highlights an important uncertainty in available study data – *"..no studies in the literature have presented information on the relative contributions of Pb from different PM size fractions to blood Pb concentrations*."
- pp. 4-5 to 4-6. Good addition of how IEUBK can be used to address questions about pathway contributions by using empirical data combined with modeling assumptions. Importantly, it highlights the challenge in estimating the portion of soil/dust ingestion that derives from air Pb, and how a sensitivity analysis was conducted to establish plausible ranges of pathway-specific contributions to blood lead from recent air Pb exposures.

Section 4.1.2 Environmental Exposure Assessment Methodologies

- p. 4-7 to 4-8. This section provides a very useful transition between the conceptual model and the discussion of exposure studies. It provides a balanced discussion of both monitoring and modeling techniques, and sets the stage for using both to inform the exposure assessment.
- p. 4-8. AALM is introduced here. For consistency with subsequent reference on p. 4-119, state that AALM is still in development.

Section 4.5.1. Air lead-Blood Led Relationships

- Figure 4-22 is an extremely helpful addition to accompany the slopes presented in Table 4-11. The descriptive text on p. 4-101 is also well written.

Section 4.6. Biokinetic Models of Lead Exposure-Blood Lead Relationships

Earlier in Section 4.3.6, Figures 4-12 and 4-13 provide graphical summaries of blood-lead and tissue-lead relationships based on simulations with the ICRP Pb biokinetics model (Leggett). In Section 4.6, IEUBK is introduced as a tool for establishing relationships between exposure-blood lead relationships. Consider adding a series of graphics that directly address the question of air-lead / blood-lead relationships (as discussed above). For example, Figures 1 to 3 below were generated with IEUBK and illustrate the potential changes in the GM and 95th percentiles (assuming lognormal distributions with GSD =1.6) if the standard were reduced from 0.15 $\mu g/m^3$ to 0.10, 0.05, or 0.015 $\mu g/m^3$.

If the standard were reduced to 0.10 µg/m^3 (Figure 1), blood-air slopes in the range of 3 to 9 would be expected to shift the distribution down by less than 1 ug/dL for both the GM and 95th percentile. Similarly, if the standard were reduced by an order of magnitude to 0.015 µg/m^3 and the slope is expected to be no greater than 7, the GM would be reduced by ≤1 ug/dL and the corresponding 95th percentile would be reduced by ≤2 ug/dL. Presenting these calculations would frame the discussion of the supporting data as falling within a range that would be expected to yield changes in blood leads within a quantifiable interval.

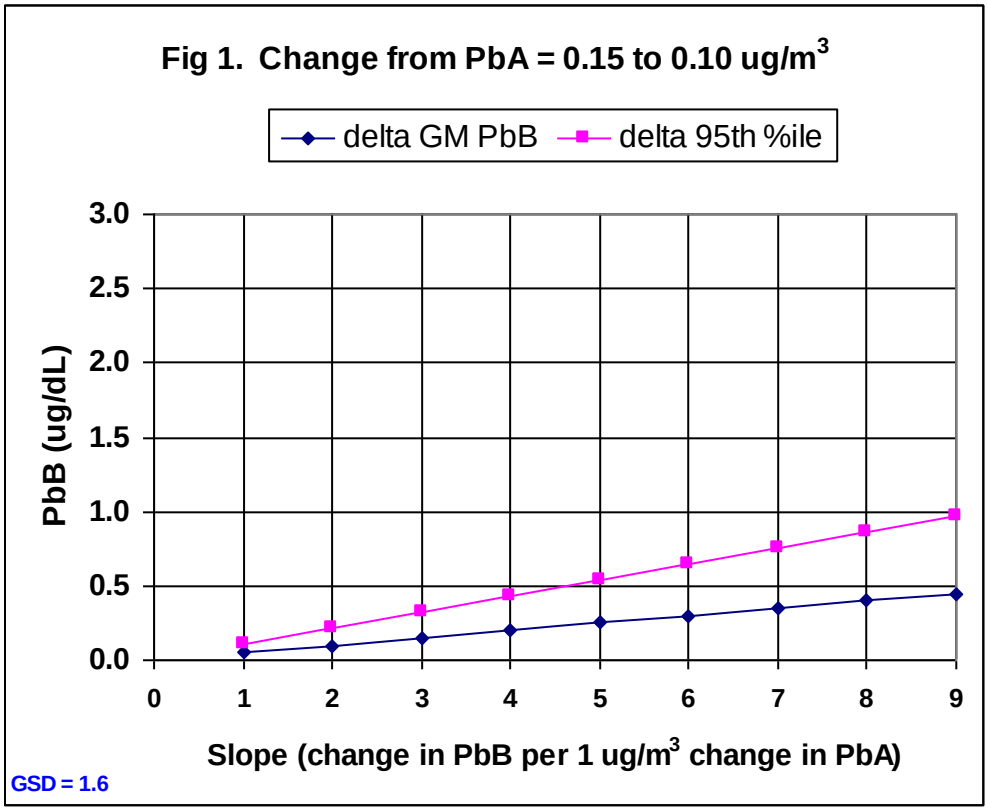
Fig 1. Change from PbA = 0.15 to 0.10 ug/m3
delta GM PbB
delta 95th %ile
PbB (ug/dL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
8
9
Slope (change in PbB per 1 ug/m3 change in PbA)
GSD = 1.6

1

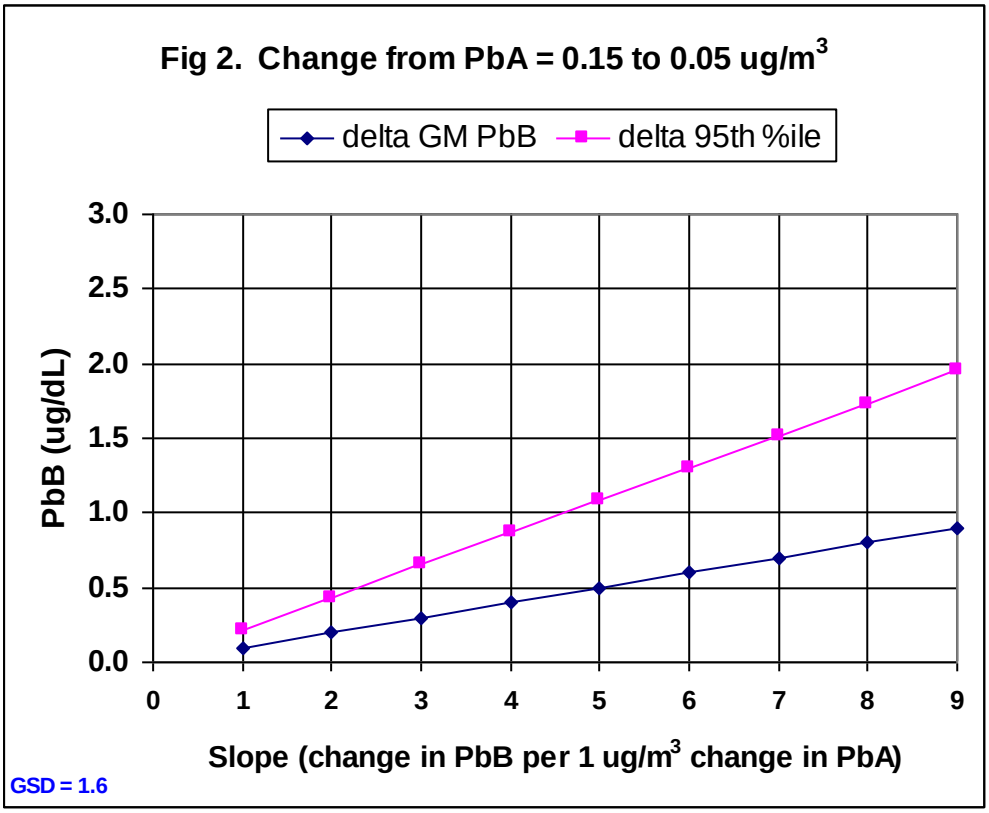
Fig 2. Change from PbA = 0.15 to 0.05 ug/m3
delta GM PbB
delta 95th %ile
PbB (ug/dL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
8
9
Slope (change in PbB per 1 ug/m3 change in PbA)
GSD = 1.6

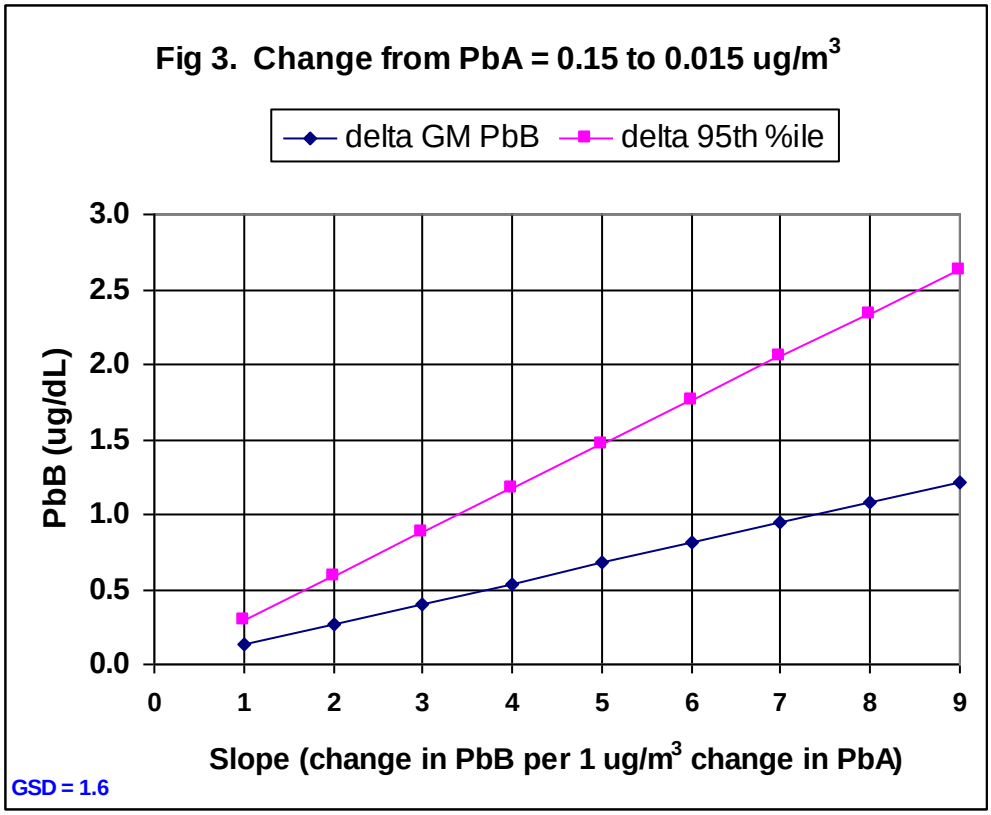
Fig 3. Change from PbA = 0.15 to 0.015 ug/m3
delta GM PbB
delta 95th %ile
PbB (ug/dL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
8
9
Slope (change in PbB per 1 ug/m3 change in PbA)
GSD = 1.6

Dr. Sean Hays

Comments on Chapter 4

I commend EPA for addressing the concerns I had with the previous version of Chapter 4. They have improved the transparency in the discussion and documentation of the Pb air-Pb blood correlations. They also expanded a discussion of the relative contributions of the various Pb sources/pathways towards PbB. A few specific comments:

- Summary of air-blood lead correlations is a helpful addition. Table 4-11 and Figure 4-22 are very helpful. It would be helpful for EPA to opine on which correlations will be most applicable for a risk assessment for air concentrations at and below the current NAAQS. The shape of the response curves are very divergent at low air concentrations, with the log-log models being the most divergent. EPA should conduct an independent analysis of the underlying studies and determine if a common model (linear, log-linear, or log-log model) can be used to describe all the datasets equally well. I would expect this to be an important discussion in the Exposure and Risk Assessment report released later this year.

- I appreciated the expanded discussion of the use of the IEUBK model to assess relative contributions of exposure sources/pathways towards blood lead concentrations for various percentiles of exposures (pages 4-5 – 4-6) and notations of expanded results available in Appendix I of the 2007 Pb Risk Assessment. This type of analysis will be critical for the Exposure and Risk Assessment report released later this year.

Dr. Philip Hopke

Comments on Chapter 3

This chapter is improved from the prior version, but there remain some problems that need to be addressed. However, much of the discussion is still largely encyclopedic where individual papers are summarized rather than providing an integrated science assessment with references to these details in an appropriate appendix. It made ready things like section 3.5 difficult since there was no integrating train of thought.

If we are to have a two-tiered sampling system (hi-vol TSP and low vol PM10), then there has to be an adequate discussion of the comparison of these two and the interrelationships that exist (to the extent they do) that can be extracted from existing data. There was some of that in the prior version that now has disappeared. Choi et al. (2011) is already in the ISA and can be used to inform this review of what we do know of particle size and lead concentrations. It is strange that it is not used since coauthors include ORD and OAQPS staff members. They need to lay the foundation for the FRM approach here.

There needs to be a greater attention paid to wheel weights. Very recent work in NJ, (Aucott and Caldarelli, 2012) based on extrapolation of their results to the entire state, suggests that approximately 12 tons per year of lead in the form of wheel weights are deposited on New Jersey roadways, and that approximately 40 kg of lead enters the environment in the form of small particles formed from the abrasion and grinding action of traffic on weights deposited on roadways. George Allen has previously commented on this issue, but the importance of this source has not yet been adequately reflected in the ISA text.

Sampling/Analysis

One sampling approach that has not been included is passive samplers such as the UNC sampler (Wagner and Leith, 2001a,b,c). Analysis of these samples is then conducted using computer-controlled scanning electron microscopy (CCSEM) (Hopke and Casuccio, 1991). The resulting data can be manipulated to provide quantitative assessment of microscale variability (Hopke, 2008). Given that the interest in lead concentrations is on a long term average value, the passive sampler provides an opportunity for dense spatial sampling designs to really explore the intra-urban variability of lead exposures across a community.

Intra-Urban Spatial Variation in Non-Source Areas

There are two reports of the variability of coarse particles across urban areas (Rochester and Syracuse, NY) where particle types that include Pb-bearing particles (Lagadu et al., 2011; Kumar et al., 2012). Thus, it would be easy to carefully examine the variability of coarse Pb-bearing particles across these urban areas relative to major roadways or other locations of interest and provide more information on spatial and temporal variability than is available from the limited number of active samplers in the

locations that are reported.

I still believe the presentation of the Spearman correlation coefficients provides absolutely no useful information. Others on the panel think Spearman provides information, but given the extensive work I have done on air quality data analysis methods, I do not agree. The fact that two variables are in the same rank order does not provide the same level of information about their co-emission as a parametric correlation like a Pearson correlation. It really tells us nothing about the likelihood that the Pb is related to the other pollutants since it could be driven entirely by meteorology such as variations in the mixing heights. It appears that they will be included, but if they are there, there certainly should be the inclusion of the corresponding Pearson coefficients so we can see the differences. These results certainly should not be emphasized in the chapter summary (section 3.7.4).

References

Aucott, M. and Caldarelli, A. , 2012. Quantity of lead released to the environment in New Jersey in the form of motor vehicle wheel weights. *Water, Air, & Soil Pollution*, 223:1743-1752.

Cho, S.-H. , Richmond-Bryant , J., Thornburg, J., Portzer, J., Vanderpool, R., Cavender, K., Rice, J., 2011. A literature review of concentrations and size distributions of ambient airborne Pb-containing particulate matter, *Atmospheric Environment* **45**, 5005-5015.

Hopke, P. K., 2008. Quantitative Results from Single-Particle Characterization Data. *Journal of Chemometrics* **22**, 528-532.

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Dr. Chris Johnson

In my review of the 2nd Draft ISA, I focused my attention on chapters 3 and 7. I hope to have additional comments, particularly on Chapters 1 and 2 at the CASAC Review Panel meeting on April 10-11.

Comments on Chapter 3

Chapter 3 of the 2nd Draft ISA is generally well written, as was the first draft. The deficiencies in the first draft have largely been addressed. While there are a few issues that panelists are likely to raise, this is a very impressive summary of the sources, transport and fate of Pb in the environment.

Question: *Please comment on the adequacy of … [the] changes to the chapter and recommend any revisions to improve the discussion of key information?*

The discussion of the limitations of current and alternative methods for measurement of total suspended particulate Pb is a good addition and strengthens the document. I will leave it to others with more expertise in atmospheric physics and chemistry to comment on the quality of these amendments. Similarly, the editing of questionable data appears to have made for a more cohesive discussion of national trends.

The addition of section (3.5.5) on background Pb concentrations is a good idea. However, I think it needs some work. The issue of how to define "background" is never fully resolved. In the first paragraph, the policy relevant background (PRB) is defined as "those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America. This definition contrasts with the more scientific definition of a "natural" background, unaffected by any anthropogenic sources. Both are difficult to assess, but the natural background is probably easier. In any event, the section never actually comes to a conclusion on what the background levels might be. The section is comprised of several paragraphs explaining why it is so hard to estimate PRB levels. Surely it is possible to bracket a range for background airborne, soil and aquatic Pb concentrations.

The additional work done on section 3.6.1, relating soil Pb to air Pb is very useful.

Question: *Is material clearly, succinctly, and accurately provided?*

The material presented in Chapter 3 was, I thought, generally accurate, complete and relevant. It is clearly presented. It is hard to call a 200-page chapter "succinct," but this is a complicated topic, and to a certain extent, the CASAC demanded the level of detail found in this second draft document.

Question: *…provide guidance that may refine the scientific interpretation and/or improve the representation of the science.*

In the areas of my expertise – soil and water chemistry – Chapter 3 does an excellent job in laying out a clear conceptual model for the behavior of Pb. I have no recommendations for refinement at this time.

Comments on Chapter 7

Chapter 7 of the 2nd Draft ISA is also nicely organized and well-written. I focused most my attention on the areas of terrestrial systems and ecosystems-level issues. The changes made to these sections of Chapter 7 add some valuable depth to what was already a generally good survey of the literature.

Question: *Please comment on … various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information?*

The two most notable additions to the terrestrial effects sections of Chapter 7 were: (1) additional discussion of ecosystem receptors and the Biotic Ligand Model; and (2) increased discussion of ecosystem services. These are welcome additions, though the application of the receptor concept in terrestrial systems is difficult to generalize across biomes.

As I commented on the previous draft, the discussion of ecosystem services in the case of terrestrial Pb is contextual. Terrestrial soils provide a service to aquatic ecosystems by sequestering Pb through sorption and coprecipitation. At the same time, this very process potentially damages services that the same systems provide, such as agricultural production. What is in the 2nd Draft ISA is valuable, but only tells half of an admittedly complicated story.

Dr. Susan Korrick

Overall Comments and Considerations:

In general, Chapter 5 of this 2nd draft Pb ISA addressed a number of the comments made in review of the 1st draft. However, some key concerns from the 1st draft are either incompletely or inconsistently addressed.

Specific areas of improvement include: (1) identifying the state-of-knowledge as of the 2006 AQCD as a baseline upon which to build; (2) improving the integration of toxicologic and epidemiologic literature both in terms of the relevance of outcomes (e.g., drawing parallels among homologous or related measures in animal models and human studies) and exposure levels (e.g., identifying studies of animal exposures within range of contemporary non-occupationally exposed populations and acknowledging limitations to dose-response implications of exposure routes that are not representative of human exposure as, e.g., intraperitoneal injection). Of note, in some cases, establishment of homologies among animal and human studies was done well but, in some cases, this effort still needs revision; (3) more explicitly discussing exposure timing and its implications; and (4) acknowledging limitations in interpreting associations with current blood Pb levels (especially in adults and older children) as such levels may not represent the exposure levels responsible for observed associations. In addition, some sections of this revision have been re-organized to improve readability and interpretability – e.g., presenting data in some tables ordered by exposure level and cohort.

While assessing the overall quality of the Chapter and its responsiveness to previous substantive concerns, it is challenging to follow-up on how the revision addresses more specific reviewer comments from the 1st draft because of the tremendous breadth and detail of material presented (~500+ pages). Also, where previous reviewer recommendations have not been followed, there appears to be no mechanism for understanding why this was the case. Some previous recommendations based on factual inaccuracies were not corrected (e.g., see summary of Kim et al. 2009b [p. 5-62 to 63, figure 5-3] where blood Mn units are reported in μg/dL but should be μg/L. As currently reported, these Mn levels are substantially higher than Kim et al. and higher than reasonable expectation and thus bring into question the study's interpretation). Lastly, in a few sections, it appears there has been editing such that some text has lost logical progression, material is out of order, phrases appear to be cut short, or inappropriate terminology is used. In the extreme, sentences and content appear to have been re-arranged in such a way that the text no longer makes sense (e.g., see the discussion of Pb and ALS on page 5-164, lines 20-36).

Chapter 5 Charge Questions:

1. *Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.*

This revised (2nd) draft does a better job than the 1st draft reflecting the weight of evidence in causal determinations but this effort still needs more work and the quality of the revision re. this issue varies widely by health outcome. For most sections of the Chapter, there is a synthesis of findings that are consistent across the literature on a topic but it's often done without attention to variable quality among studies. Instead, the "weight of evidence" analysis often seems to be based on the number of studies on a topic or the predominant finding(s) among available studies but does not consistently include design critiques of those studies. Indeed, in much of the Chapter not only are analyses of strengths and limitations absent but basic information such as study sample size is not mentioned in describing study findings. In much of the Chapter, there are not analyses of which studies contribute the most robust evidence and which do not with conclusions based on the more robust findings. Some new studies have been added and weak ones (e.g., case reports) removed which are appropriate updates. However, in other cases, null studies or studies that do not support the Chapter's conclusions are either not reviewed or only reviewed cursorily. Although there is some discussion of strengths and limitations of studies for some studies and some outcomes, in other instances (e.g. the description of Pb's associations with puberty) there is essentially no discussion of study design issues despite the clear potential for uncontrolled confounding, selection bias, or cross-sectional study design to impact the strength of findings in many, if not all, studies reviewed for this outcome. Similarly, in the review of child neurodevelopmental literature there is not much discussion of how study design limitations might impact the weight of evidence (e.g., there is limited, if any, discussion of the relative value of cross-sectional vs. longitudinal analyses or self-reported diagnosis in studies of ADHD or attention-related measures) whereas the review of adult neurodegenerative disease more consistently acknowledges study design issues (e.g., potential reverse causality in cross sectional or case-control studies).

2. *Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiological studies, in particular: the increased emphasis on toxicological findings most relevant to Pb-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Pb-associated health effects. (a) Has coherence of findings among related endpoints been sufficiently described? (b) Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.*

In general, this revision integrates toxicology and human literature more effectively than the 1st draft by having a clearer focus on homologous/parallel outcomes between the animal and epidemiologic literature. E.g., in the discussion of nervous system effects, animal assessments are explicitly described in terms of which human assessments they parallel (there's an example of this on p. 5-99 in the discussion of cognitive flexibility). Similarly, mechanistic toxicity/mode of action studies are discussed

in terms of relevant human effects. Also, there is more discussion and explicit description of exposure levels in the toxicology literature reviewed (e.g., inclusion of blood Pb and, in some cases, even bone Pb levels in animals) so relevance to human exposures can be more clearly delineated. As per the above general comments, coherence of findings across human and toxicologic literature has generally been better specified than in the first draft. But, in a few instances, this still needs work. For some outcomes, a number of the animal studies reviewed had exposures well in excess of those typical of current human populations; the applicability of these findings to humans (e.g., to provide mechanistic insight vs. dose-response information) was not consistently addressed. In some areas, homologies across animal and human studies may have been identified incorrectly. In other instances, integration is incomplete. E.g., for some immune effects, the most robust associations are based on the toxicology literature, not the human literature. This distinction is not clear in the text. Pb-associated changes in cytokines is listed as an association supported by the literature (p. 5-389) whereas elsewhere (p. 5-386), the text states "… it is difficult to draw conclusions about…effects of Pb on cytokine[s]…in human population[s]. This is an example of apparent inconsistencies across the two literature sources that need to be more clearly acknowledged and their implications discussed. There are a number of design limitations in the epidemiologic studies reviewed for immune system effects and these might account, in some part, for lack of concordance with toxicologic data but these limitations are not reviewed. Apropos of this issue, some discussion of whether or not animal and toxicology literatures are sufficient to support causality in the absence of consistent findings in the human literature is needed

3. *Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). (a) Are inferences regarding the specific Pb exposure scenario (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?*

Generally, this revised draft is careful to distinguish between settings (based on study design, study population, etc.) in which a given Pb exposure level (in blood or bone) is likely associated with a particular health outcome and settings in which a given Pb exposure level may not directly account for observed health effects because of the possible contribution of previously elevated or longer term exposures. Likewise, there was clear acknowledgement that blood Pb in adults includes information about past exposure (via bone Pb mobilization, e.g.). However, apropos of charge item #2 above, there were some instances of an apparent disconnect between relevant exposures in human as compared to animal data. E.g., for neurodevelopmental toxicities, there was a recurrent theme of prenatal/early life exposures being key to Pb neurotoxicities in developing animals whereas a number of recent human studies suggest that concurrent (later childhood) Pb exposure may be the most toxic. This seeming discrepancy and the possible risk represented by concurrent childhood blood Pb (especially in the context of early life exposure) was not addressed clearly.

Specific Comments:

NERVOUS SYSTEM EFFECTS

Page 5-79: How does "past exposure via maternal bone Pb" impact cord blood? Is this comment assuming there were higher exposures in earlier pregnancy prior to delivery absent some exogenous exposure source? Are there data to support this? E.g., calcium demands in pregnancy, especially early in pregnancy, are relatively small (e.g., compared to lactation) so differential effects on Pb mobilization across pregnancy seem unlikely.

Page 5-53: Removed case study from this section which is good but same concerns as with 1st draft. MRI studies cited include children (ages 9-13), some cross-sectional analyses, so description of "young adults with prior childhood Pb exposures" (Cecil et al. 2005) does not seem accurate.

Figures 5-2 & 5-3: BPb levels and effect estimates look different for some studies compared with 1st draft, not clear what changed or why (e.g., used concurrent vs. lifetime exposure effect estimates for Canfield et al., 2003a?)

Page 5-63, figure 5-3: As with 1st draft, Mn units should be mcg/L not mcg/dL. This matters since, otherwise, it looks as if Mn exposures were enormous in the population and interpretation of relative Pb contribution is more complicated.

Page 5-64: Try to consistently provide Pb exposure levels, not done for some studies (Kordas et al, 2011; Roy et al., 2011)

Pages 5-66: Apparent and repeated emphasis on HOME as a key confounder throughout this section seems misdirected (e.g., see page 5-102). Clearly HOME is important but a broader and more balanced discussion of confounding overall would be more useful. HOME is just one component of a large number of key potential confounders for child nervous system effects.

Page 5-68: Moffitt et al., 2001 should be Jedrychowski et al. 2009a; line 7 insert larger *decrease* in MDI

Page 5-69: It is unclear what text is saying about interaction between Pb and folate in determination of MDI effects. Does folate lower blood Pb levels or decreased target tissue sensitivity to Pb's toxicity at the same level of exposure? Importance of distinction between exposure modification and effect modification seems blurred.

Page 5-78: Five Korean studies (should be *cities*?) with null findings but didn't give reference or BPb levels….need reference Cho et al., 2010.

Page 5-100: No chelation discussion for humans? Is succimer trial in moderately exposed children too old (main result NEJM 2001)?

Page 5-101: Weight of evidence "based on frequency of examination", what does this mean? In this section and elsewhere, some discussion integrating what's known about critical exposure periods in epidemiologic literature and what current thinking is re. the meaning of concurrent blood Pb and its association with cognitive function in children would be helpful. E.g., is there some 'acute' blood Pb effect postnatally? Is high concurrent blood Pb a proxy for identifying children with consistent high Pb exposures over time? Or something else?

Page 5-117: PbxGene interaction commentary for adult cognitive function: "Results were ***NOT*** uniform across…cognitive tests…"

Page 5-119/120: Recent studies looked at concurrent BPb – distinction between cross-sectional vs. prospective designs not always clear. Cannot always infer that concurrent BPb is most potent if lack information about earlier life BPb levels and their relationship with behavior outcomes. Text is unclear on this point although this does not mitigate importance of concurrent exposure, always must consider the possibility of reverse causation.

Page 5-120, lines 11 & 15: Should be increases in ***inattention***, not attention…or ***"increased inattention"***

Table 5-10: Several NHANES analyses for ADHD diagnosis – ADHD diagnosis in NHANES from parental report (+/- medication use). Limitations of this outcome measure should be mentioned. E.g., outcome reporting bias, outcome measurement error, and possible confounding by regional differences in diagnosis (there are differences in medical practice by regions in the U.S.) and regional differences in Pb exposure risk.

Page 5-132: Do not understand logic of statements re. confounding for ADHD analyses. Specifically, for parental ADHD to be a confounder of Pb-ADHD behavior, parental Pb does not have to be highly associated with parental ADHD (which is in current text). Given the strong familial component of ADHD risk, parental ADHD would only have to be correlated with child Pb to be a confounder.

Page 5-142: Opler et al. (2004, 2008) assessing schizophrenia using δ–ALA level as a proxy for BPb (>15) is an important outcome but limitations of exposure assessment and how to integrate these studies into the context of this document need to be clear.

Page 5-155: This page is one example of an issue that comes up elsewhere: units for bone Pb measures in animals are incorrect. This impacts the interpretability of the exposure information. Units are reported incorrectly as μg/dL whereas they should be μg/gm bone mineral.

Page 5-160: Pb effects on retina "are modified by dose of Pb" seems an odd way to describe the literature. Was this meant to indicate that a number of the Pb-associated changes in vision in the toxicology literature do not follow a monotonic (or even threshold) dose-response? If so, say so, and then discuss what these atypical dose-response relationships might mean, if they are biologically plausible, and, if not, if that undermines the robustness of any observed associations.

Page 5-165: The motor section, last paragraph looks as if it's been cut and pasted so it no longer makes sense (plus punctuation problems). "The collective body of evidence demonstrates that within the same population of children…" doesn't make sense. Where are the "observations that Pb exposure affects development and function of …[motor]…systems"?

Page 5-162: The description of findings re. seizures in animal models doesn't explain the basic experimental study design/premise before jumping into results so the text is hard to follow– this happens several times throughout descriptions of the animal literature for nervous system effects.

Page 5-164: For ALS, discussion of potential for differential survival time to bias Pb association is very confusing. It is impossible to follow the argument, I suspect something was edited in a way that muddled content.

Page 5-167: line 12 – replace PD with ET.

Page 5-168: The discussion of the toxicology literature's evidence of a possible role of of microglial cells in neuro-inflammatory processes is confusing, talks about two cell types without specifying which two cell types are intended. Was text cut and pasted into the wrong place?

Page 5-169: Toxicologic evidence of Pb-induced cell apoptosis is largely observed at very high exposures; this issue is not acknowledged and its potential relevance, or lack of, to current population exposures is not mentioned but should be.

Page 5-170: Incongruities between epidemiology and animal studies of Pb and AD may not just be because of wrong exposure time (i.e., developmental exposure matters most and epidemiology largely relies on adult exposure measures). Even recent animal studies are largely conducted at doses well in excess of expectation for current non-occupationally exposed aging adults. The potential role of exposure level on incongruities is not discussed but should be. Are authors assuming a non-threshold effect? If so this should be discussed and explained. This is an example where integration between toxicology and epidemiology literature could be improved.

Page 5-191 (lines 20-21): comes up elsewhere in text, language is confusing re. meaning of "maternal Pb exposures"; here presumably mean maternal *pregnancy* exposures/Pb levels, otherwise it is not clear how maternal Pb exposures *postnatally* are contributory to offspring lower cognitive function.

Page 5-191 (lines 27-28): expected correlation between prenatal and postnatal blood Pb likely depends on how far from birth measures are made – e.g., 3-month vs. 15-month old infant? See page 5-196 for an apparently contradictory text describing example of weak correlation between prenatal and subsequent blood Pb levels.

Page 5-212: Causal pathway usually refers to inter-related health outcomes, not over controlling for exposure proxies.

Page 5-219: Clarify what's cross sectional and what's prospective for ADHD studies.

Page 5-221: For line 18 should "temporality" be "directionality"?

Page 5-224, lines 23-27: Cannot say weight of evidence supports concurrent exposure as most deleterious and then in the next sentence indicate that considerable uncertainty exists on critical exposure period. Latter seems the better conclusion.

CARDIOVASCULAR EFFECTS

Page 5-236: In description of findings in occupational cohort in Korea it may be worth noting that the population is young and potential for bone Pb-BP (especially HTN) findings in older populations to, at least in some part, reflect confounding by age (since bone Pb is generally strongly correlated with age) is not discussed.

Page 5-244: acknowledge that injection Pb administered in animals may not be comparable to human exposures

Page 5-265: It is true that there are few studies of Pb and CVD effects other than BP or HTN (e.g., HRV, PAD, IHD) but it is also the case that much of data is from only 2 population sources (NAS and NHANES; see Tabel 5-19) which is another useful caveat.

Page 5-282, lines 36-37: Findings across studies are not as consistent as this sentence implies: e.g., Pb-associated stroke mortality not elevated in SOF (Study of Osteoporotic Fractures)

Table 5-21: Neuberger et al., Cocco et al. Not discussed in the text? Used SMRs and found protective SMRs in latter study, a follow up of an occupational cohort of Pb smelter workers– some discussion would be useful. Is this an appropriate study to include, i.e., how high were exposures and are design issues including the potential for a healthy worker effect important limitations?

RENAL EFFECTS

Page 5-308: Issue of reverse causality is the same as before: especially in a cross-sectional analysis, seeing a stable Pb-serum Cr relationship across the normal range of serum Cr does not rule out reverse causalitiy as there can be substantial decrements in renal function with 'normal' serum Cr….Also (see Table 5-25) NAS longitudinal studies adjusted for baseline serum Cr which can bias results assessing change in Cr.

General issue (but evident in renal section): Where susceptible subgroup analyses are done (e.g., by genes like HFE or by health status/co-morbidities), although the interaction may be biologically plausible, there's always the possibility that subgroup findings are by chance especially if the subgroup is small. E.g., in Tsaih et al. the Pb-Cr findings in the NAS population are strongest in diabetics (n~26?). It's important to consider this limitation in interpreting findings.

Page 5-327-28: Discussion of why reverse causality is unlikely to explain Pb-renal function associations is a useful addition but it lacks balance; that is, it would be an even more useful addition to the chapter if it acknowledged that reverse causality is still possible in epidemiologic studies of Pb and renal function.

Page 5-339 (section 5.5.5.1): Re. renal effects and the impact of 'treatment' with antioxidants is presented in an awkward context – is this intended as a summary of 'treatment' interventions? Or as a commentary on Pb MOA?

IMMUNE SYSTEM EFFECTS

Page 5-366: Cross-sectional studies in adults are not just limited because of uncertainty re. relevant Pb exposure dose and time period. There are also important limitations due to potential confounding and challenges with potential reverse causation. E.g., it's speculative but theoretically possible that adults with inflammation may absorb Pb more efficiently.

Page 5-367: IgE and Pb: only at the end of this section is there acknowledgement of limitations in the literature due to lack of control for confounding (especially important in childhood studies is failure to account for potential confounding by SES or allergen exposure, e.g.). It would be useful to discuss this issue more systematically during the literature review; otherwise, the relative value of different studies is hard to judge. Also, where studies are cross-sectional (which is a common limitation of the immune studies reviewed), this design limitation needs to be mentioned. (See above comment re. attendant caveats with cross sectional designs including the possibility of reverse causality. E.g., as above, one could speculate that children in a pro-inflammatory state might absorb Pb more efficiently such that immune changes lead to higher blood Pb rather than the reverse).

Page 5-368: Here and elsewhere in the Chapter "lack of statistical analysis" is used, this phrase needs to be defined.

Page 5-372: This issue comes up in several places in this Chapter, that is, there is a caveat given that higher past Pb exposure may have influenced maternal pregnancy Pb levels and resultant fetal exposures. When looking at newborn outcomes, it's not clear what this means. Maternal pregnancy Pb levels are what the infant experiences, not maternal past Pb exposures. Is the issue that, somehow, past maternal Pb exposures influence variability in Pb levels during pregnancy? Whatever the issue, it needs a clearer explanation.

Page 5-378: The title for section 5.6.5 – "Mode of Action for Lead Immune Effects" is confusing as inflammation itself an "immune effect". Perhaps there needs to be a clearer distinction between Pb effects believed to be mediated through immune toxicity (e.g., asthma) versus direct effects of Pb on measures of immune function?

Page 5-383-84: In describing the relation of Pb with cytokines, studies which are concordant with a particular conclusion (e.g., Pb-associated depressed Th1, enhanced Th2 response) are emphasized with

inconsistent findings cursorily described (e.g., "other studies found variable Pb-induced changes in IL-2"). It is impossible to discern whether this was an oversight, a biased presentation of the available literature, or an attempt to prioritize findings based on the quality of the studies reviewed since quality/study design issues are not discussed.

Page 5-384: The need to make analysis of the literature as independent and balanced as possible is illustrated here where authors conclude that differences in cytokine levels among healthy and allergic children living near an oil refinery may have been due to differences in blood Pb levels. Presumably there are other issues that could explain the observed associations in this study given limitations in its design; perhaps most important of these is potential confounding by other exposures associated with residence near a refinery which is not acknowledged in this discussion.

Page 5-386 (lines 26-27) What's "limited" about the investigation of Pb and cytokines? Number and/or quality of epidemiologic studies? Or is it that findings are not consistent? This broad statement needs better definition.

Page 5-389 (~line 18): Listing Pb-associated changes in cytokine production among associations supported by the literature seems to contradict conclusion on p. 5-386, lines 27-28 that "it is difficult to draw conclusions about …effects of Pb on cytokine(s)…in human population(s)." In addition, a number of epidemiologic studies reviewed in this section lacked adjustment for important potential confounders and were often cross sectional, a design that limits inferences that can be made re. the direction of the association. These are examples of substantial limitations in the human literature but these limitations are not reflected in the summary. Similarly, some discussion of whether or not animal and toxicology literatures are sufficient to support causality in the absence of consistent human literature is needed.

Page 5-391, lines 3-6: This section is an example of an important limitation that comes up throughout this Chapter. That is, cross sectional studies are acknowledged for having "uncertainty regarding the magnitude, timing, frequency, and duration of Pb exposures that contributed to the observed associations" but rarely acknowledged as being limited regarding the direction of the association or, depending on the design (e.g., case-control studies) being limited by potential sources of selection bias or confounding. As above, in the case of immune function measures, it's theoretically possible that individuals in a pro-inflammatory state absorb Pb more efficiently. Thus immune changes could induce higher blood Pb rather than the reverse; it is difficult, if not impossible, to distinguish these two possible directions of effect in most cross sectional studies.

Page 5-392, lines 28+: Lack of confounding in one study design does not mean that failure to adjust for potentially important (identified a priori) confounders in another study design is ok. Confounding patterns, by definition, can be study specific (depending on study design and population).

HEME SYNTHESIS AND RBC FUNCTION

Page 5-398: It is important to acknowledge potential confounding by other occupational exposures in occupational cohort studies (here re. heme synthesis/RBC toxicities) but similar attention to this issue is not consistent in this Chapter (e.g., not done in immune function section).

Page 5-401, lines 14-16: Is the issue "equivocal findings" or inconsistent findings? It seems most studies have unequivocal findings, they're just not all in the hypothesized direction. Differences among studies of children could also have to do with residual confounding or other design limitations.

Page 5-411, lines 27-33: In vitro studies described as having "similar effects on indices of oxidative stress" are presumably being compared to Conterato et al.? However, the latter observed some Pb associations in the opposite direction (e.g., associations with SOD) of those described for in vitro studies. Given the complex feedback among some of these measures, this needs clarification.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Page 5-431, ~line 103: For epidemiologic studies of puberty reviewed here potential confounds of associations are not discussed – e.g., nutritional confounding could be very important to these associations especially in populations where malnutrition may be common (e.g., Tomoum et al.).

Page 5-431, lines 8+: Better clarity on the direction of described associations is needed. Presumably, Naicker et al.'s positive association of blood Pb and age at menarche, etc. was a positive association with ***delayed*** age at menarche. The current text implies the opposite association.

Page 5-437 (table 5-34): It is notable that in this table and elsewhere in section 5.8, information about confounding adjustment and study sample size is rarely, if ever, provided. This should be included as part of the balanced review of the strengths and limitations of the literature. E.g., statistically significant findings from a small study are more likely due to chance than findings in a large population. Similarly, wide confidence limits may reflect lack of power from a small n where moderate to large effect sizes are observed.

Page 5-450: The same comment applies to studies in men and women – use of study populations being treated for infertility is not just an issue of generalizeability of findings. It is also potentially the case that bias (e.g., participation bias) and related design limitations could impact robustness of findings.

Page 5-454, lines 3-4: "delayed pubertal development" should be "delayed pubertal onset"

Page 5-454, lines 4-5: Ages appear to be reversed.

Page 5-466: As is true of most, if not all, of this section, review of literature on Pb and pre-term birth was done without any critiques so the conclusion that no patterns of findings were apparent seems premature. E.g., it is possible that, among the studies reviewed, those with better design and higher Pb

exposures have more consistent associations with preterm birth. However, it is not possible to ascertain this kind of pattern without more systematic assessment of each study's relevant strengths and weaknesses as well as assessment of the potential for there to be a threshold for a Pb effect.

Page 5-472, lines11-12: "..the strongest associations observed at the lowest blood Pb level…" is a confusing statement especially given the data presentation in Table 5-40. Is this statement meant to refer to a supralinear dose-response? If so, it would be clearer if describe that way.

Page 5-476, Table 5-41: Afieche et al., effect estimates need a '-' sign.

Page 5-484: What does it mean to have decreased hepatic DNA?

Page 5-486: Not clear why authors conclude Pb-delayed puberty associations are stronger in girls than boys. There are fewer studies among boys but their findings are relatively homogeneous and, although not strictly comparable, effect estimates seem roughly comparable to those observed in girls.

EFFECTS ON OTHER ORGAN SYSTEMS

Page 5-489, lines 18-19: Previously described associations of increases in liver enzymes with occupational Pb exposure but not "specifically with Pb exposures" does not make sense. Is this referring to studies for which occupation rather than a biomarker of Pb exposure was used to estimate exposure? If this is the case, as is described later in this section, the role of confounding by other occupational exposures may be particularly relevant in interpreting such literature.

Page 5-493, lines 31-33: Is apparent differential effect on CAT activity (increase with Pb, decrease with undernourishment) correct? Section as written implies the effects of Pb and malnutrition are similar; additional explanation would be useful.

Page 5-506, lines 30-34: It is unclear what the meaning of this finding is vis-à-vis Pb's association with periodontal disease as it is not based on assessing the relation of a biomarker or other indicator of Pb exposure with the outcome. The value/context of including this study in the review needs to be made clear.

Page 5-510 (and 5-503): As with studies of Pb and bone/joint turnover markers, NHANES analyses of blood Pb and osteoporosis are also limited by cross sectional design so the direction of the association is uncertain.

CANCER

Table 5-42: Need to provide explanation for effect estimates, e.g., SMR's, OR's, HR's or whatever measure was used for each study. Only 2 studies in the entire table seem to have this information. Also, something is wrong with Lundstrom et al., units for median cumulative blood Pb index – µmol/Pb cannot be correct.

Page 5-521, lines 1-2: As in above comment re. Page 5-437, study summaries for cancer outcomes generally lack information about sample size. This should be part of the critical review.

Page 5-526: This is an example of an issue that comes up throughout the Chapter – acknowledgement of one of the key limitations of studies in occupational cohorts, i.e. confounding by other occupational exposures, is often not discussed. This should be part of the critical review

Page 5-530, lines 19-23: As was an issue mentioned in the review of the 1st draft, for studies of chromosomal aberrations, it seems the most robustly designed and most consistent associations are with lead chromate (not acetate or nitrate) and yet interpretation of such studies is limited because of chromate's potential role in observed associations. This is mentioned in the section but should be repeated in the summary paragraph as it is an important limitation of this literature. Limitations of using Pb chromate for cancer-related studies are not consistently acknowledged throughout this cancer section of the Chapter. However, it is appropriately discussed in some sections (e.g., page 5-535, lines 5-6 and page 5-537).

Page 5-538: As per previous comment re. page 5-389, some discussion of how to characterize causality when most evidence comes from the toxicology, not the human, literature is a challenge.

Dr. Michael Kosnett

The following are comments on the 2nd external draft Integrated Science Assessment for Lead (February 2012) prepared following the CASAC Lead Review Panel meeting of April 10 -11, 2012. These comments focus on Chapter 2, the Integrative Summary, and Chapter 5, Health Effects.

Key elements of the CASAC Lead Review Panel report on the 1st External Review Draft of the Integrated Science Assessment for Lead included a recommendation that the ISA improve its approach to causation assessment for the health effects of lead. Specifically, the CASAC report (December, 2011) recommended, "With respect to human health endpoints, a rigorous weight-of-the-evidence assessment is needed that transparently applies the criteria for the strength of evidence for causation" and "This weight-of-the-evidence assessment should be applied to specific health endpoints, in addition to broadly assessing impacts on whole organ systems." I respectfully feel that the 2nd draft ISA has failed to satisfactorily address these major recommendations.

The "causation determinations" summarized in Chapter 2 continue to address broad organ system findings, without specifically focusing on key health endpoints within those endpoints. For example, in Section 2.6.2 (Cardiovascular Effects) page 2-18, the narrative states, "Collectively, the evidence integrated across epidemiologic and toxicological studies as well as across the spectrum of other cardiovascular endpoints examined is sufficient to conclude that there is a causal relationship between Pb exposures and cardiovascular health effects." But the summary section on Cardiovascular Effects does not specifically indicate whether the endpoints subsumed under "Cardiovascular Effects" with respect to causality includes hypertension in adults, hypertension in children, cardiovascular mortality, or cerebrovascular mortality.[1] Nor, for virtually all the organ systems, have these causation determinations identified the magnitude of lead exposure that conclusively causes specific health effects. For a risk characterization document such as the lead AQCD to have optimal utility to risk managers and public health stakeholders, identification of specific health endpoints and the exposure (or dose) associated with causation are necessary. This is well illustrated by the narratives supporting the derivation of Reference Doses in EPA's ISIS database, which identify specific doses (e.g. LOAELs) associated with specific health effects.[2]

[1] In Summary Table 2-10, specific cardiovascular endpoints such as blood pressure, hypertension, and cardiovascular mortality are addressed, but the conclusion is limited to stating that the evidence supports "an association" between lead and these endpoints. As noted further in these comments, this terminology is ambiguous with respect to causal determination, which requires more than a summary finding of 'association".

[2] The summary discussion of cardiovascular endpoints in section 2.6.2, and the corresponding section in Chapter 5, note that although some studies have found a significant association between blood lead < 5 µg/dL and cardiovascular endpoints in adults, these adult cohorts experienced much higher blood lead concentrations earlier in life. It is further noted that bone lead has been a strong predictor of cardiovascular endpoints in some studies in which current blood lead was not (e.g. the Normative Aging Study cohort reported by Hu et al, 1996). While the ISA is correct to note current uncertainty with respect to the precise cumulative lead dose associated with a given risk of hypertension, it would be reasonable to conclude that longterm (e.g. decades) of lead exposure resulting in a blood lead across the range of 10 to 25 µg/dL likely bears a causal relationship with an increased risk of hypertension in susceptible populations (cf. Kosnett M et al, Recommendations for Medical Management of Adult Lead Exposure, Environ Health Persp 115:463-471; 2007).

In addition to the lack of focus on specific health endpoints, the causation assessments included in the 2nd ISA fail to systematically address the causation criteria set forth in Table II of the preamble (p lvii). As stated in that table, a conclusion that a causal relationship exists between lead exposure and a human health effect requires that:

> "…the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators."

The summary presentations in Chapter 2, and apparently most of those in Chapter 5, generally fail to present a critical analysis, in narrative terms, that systematically addresses the adequacy with which the human epidemiological studies have ruled out the influence of bias and confounding, and the extent to which multiple high quality studies have reached consistent and replicate findings.

For example, with respect to "neurobehavioral effects" in children, Chapter 2 concludes, in Table 2-10:

> Recent studies in children continue to support associations of Pb exposure with a range of effects, largely inattention and hyperactivity, and also misconduct delinquent behavior. In new studies, *the weight of evidence supports associations* with concurrent blood Pb in populations with lower mean blood Pb levels (2–5 μg/dL) than those in previous studies. New evidence indicates associations of concurrent blood Pb levels with ADHD diagnosis and contributing diagnostic indices in populations with mean blood Pb levels 2-4 μg/dL. [emphasis added]

The terminology in the foregoing paragraph, which is repeated frequently in other parts of Chapter 2 and Chapter 5, states that the "*weight of evidence supports associations*". This phraseology is ambiguous, and fails to address the requisite elements of a "weight of the evidence" causation determination. A finding of an "association", however strong, between lead exposure and a health endpoint in an epidemiological study is by itself inadequate to establish causation, particularly if bias and confounding cannot be ruled out with reasonable confidence. As was stated in the CASAC report of December 2011:

"With respect to other [i.e. noncognitive CNS] endpoints in children, such as attention deficit hyperactivity disorder (ADHD), a more rigorous and transparent "weight of the evidence" analysis is recommended to establish the extent of any causal relationship. This analysis should devote more attention to the limitations of the existing studies with respect to consistency, reproducibility, bias, control for confounders, and shortcomings in statistical methodology."

The discussion of neurobehavioral endpoints in Chapter 2 and Chapter 5 in the 2nd draft ISA continue to lack a sufficient critical discussion of such limitations. Contrary to the recommendations of the CASAC report, the tables that describe key studies addressing specific health endpoints have not been expanded to include a column that specifically addresses key limitations of each study. With respect to

neurobehavioral endpoints in children, the narrative sections of Chapter 2 fail to note that virtually all of the studies of low level lead exposure have inadequately adjusted for parental psychopathology. This is a major limitation in studies of inattention in general and ADHD in particular, where epidemiological findings suggest that heredity accounts for 50 to 70 percent of the incidence. Accordingly, parental psychopathology, particularly parental ADHD or subclinical deficits in attention, merit major consideration as potential confounders. In contrast to most studies of the effect of lead on cognitive function in children, in which the influence of maternal intelligence is commonly adjusted for by including maternal IQ as a covariate in regression models, the studies of low level lead exposure and child behavior have been unable to include an acceptable measure of maternal or paternal inattentiveness or ADHD.[3] EPA's causation criterion requiring that confounding be ruled out with reasonable confidence has therefore not been satisfied.

EPA's causation criterion pertaining to "consistency" and "replication" by multiple high quality studies is likewise inadequately addressed in the narrative with respect to low-level lead exposure and behavioral endpoints. For example, neither chapter 2 nor the section 5.3.3 note that two major prospective studies of low lead level and child behavioral outcomes did not observe a significant association between lead and measures of attention (Wasserman et al, 2001; Canfield et al, 2003). In the prospective cohort study of Yugoslavian children in Pristina with BLL < 10 µg/dL studied by Wasserman et al (2001), blood lead was not significantly associated with either the attention subscale or the aggregate "externalizing" behavior score. In the prospective Rochester cohort of 4 to 5 year old children with mean BLL of 6.5 µg/dL studied by Canfield et al (2003), there were no significant associations in multivariable models between blood lead and performance on tasks of attention (see Table 2 in Canfield et al). In contrast, different studies conducted in these same cohorts have reported that low-level lead exposure was associated with decrements in cognitive function. Overall, the 2nd draft

[3] The narrative in Section 5.3.3.1 comments that several of the studies of child behavior listed in Figure 5-14 and Table 5-9 have controlled for potential confounders such as SES and maternal IQ, while inexplicably failing to note the lack of adequate control for parental psychopathology. As demonstrated by Chen et al (2006), maternal IQ is not a significant covariate for child behavior. On page 5-127, the ISA narrative states, "While none of the studies examined the potential for confounding by HOME score, they did evaluate confounding by several other demographic and SES- related variables, as well as parental history of psychopathology, including ADHD (Cho et al., 2010; Nicolescu et al., 2010)." However, a careful assessment of these studies would raise substantial doubt as to the adequacy with which such potential confounding was in fact addressed. In the Korean study by Cho et al (2010), which in fact *failed* to report a consistent positive association between lead and indices of ADHD or attention in most of the measures that were examined, the adjustment for parental psychology consisted of having the parents of 590 children note in a questionnaire whether they ever had ADHD or any other neuropsychiatric disorder. Implausibly, less than 5 percent responded affirmatively. Moreover, the variable was not included the multivariable models. In the Romanian study by Nicolescu, parents were asked by telephone interview whether either had been diagnosed with "psychological/psychiatric problems." However, the extent of positive response was not reported, and even though "family psychopathology" was the factor with the *strongest* bivariate correlation with child ADHD rating by the parents, it was *not* included in the multivariable models of child attention or ADHD (see caption to Figure 2 in Nicolescu et al, 2010). The statement on page 5-132 of the 2nd draft ISA that refers to Nicolescu et al by stating, "Higher blood Pb level was associated with higher ADHD ratings in children in models with blood Pb level alone and in models that adjusted for parental psychopathology plus other covariates" is puzzling and should be corrected, because it appears to be contradicted by the details of the model reported in Figure 2 of that report. The narrative on page 5-132 also erroneously states, "It should be noted that for parental ADHD to be a confounder, parental Pb levels would have to be highly associated with ADHD in the parent and with blood Pb level in the child."

ISA has failed to present a critical review that distinguishes the well-validated causal relationship between low level lead exposure and cognitive function with the comparatively smaller and limited body of epidemiological evidence that has examined the relationship between lead and behavioral outcomes. As noted by Bellinger et al (1994), compared to models of cognition, models of behavioral outcome in children explain comparatively little of the overall variance (i.e. they have low R^2), raising the likelihood that even statistically significant associations may be relatively more vulnerable to residual confounding.[4] [5]

In accordance with recommendations in the first CASAC report, sections of the 2nd draft SA in chapter 2 and chapter 5 pertaining to adverse effects of lead in adults appropriately note the effects cannot confidently be imputed to contemporary blood lead concentrations (i.e. < 10 µg/dL) because the populations in which they have been observed sustained higher blood lead concentrations in the past (i.e. general population BLLs of 10 to 25 µg/dL in the decades prior to 1980). Nevertheless for the endpoints of blood pressure, hypertension, and cardiovascular mortality, secular trends in blood lead and bone lead data would allow EPA to reasonably conclude that decades of blood lead concentration in the range of 10 to 25 µg/dL can cause elevated blood pressure and increased cardiovascular mortality in susceptible populations. The epidemiological data support this finding by virtue of consistent findings in multiple high quality studies that have adequately controlled for bias and confounding. In addition, toxicological and clinical data offer evidence of plausible biochemical mechanisms at this level of exposure.

The situation with respect to low level lead exposure and renal effects is quite different, and for this endpoint the 2nd draft ISA continues to lack a balanced and critical analysis of the strengths and limitations of the data. In its consensus response to charge questions, the first CASAC report (December 2011) noted with respect to the 1st draft ISA:

[4] The summary narrative in Chapter 2 and the expanded narrative in Chapter 5 fail to note other major limitations of many of the studies of the relationship between low-level lead exposure and behavioral problems in children. In contrast to the negative prospective studies of Wasserman et al (2001) and Canfield et al (2003), many of the "positive studies" are limited by a cross-sectional study design, combined with the fact that the single measure of blood lead available was obtained in late childhood. The cross-sectional design offers limited causal inference regarding low level lead exposure because it does not rule out that the possibility that a behavior problem preceded the development of an elevated BLL, and/or that BLL in early childhood may have exceeded the value measured in late childhood. The following sentence on page 5-127, line 4 is misleading and should be replaced: "Recent studies consistently reported associations of blood Pb levels with ADHD in children." First, it should be noted that many of the studies cited did not formally diagnose ADHD, but rather relied on screening tests for ADHD or tests of attention, which is not the same as a clinical diagnosis. Second, it should be acknowledged that not all the studies yielded consistent results using these limited testing methods. In the study by Cho et al (2010), blood lead was no longer associated with measures of attention in the continuous perfomance test after adjustment for covariates (see Cho et al, 2010, table 3). In the same study, blood lead was significantly correlated with the teachers grading of ADHD, but not the parents' grading of ADHD. In a study by Kim et al (2010) [Sci Tot Environ 408:5737-5743; 2010 – not cited in the ISA], teacher rating of ADHD behavior was not significantly correlated with blood lead after adjustment for covariates in the entire population of children (see Kim et al, 2010 table 2, model 3). A positive finding (in boys only) emerged in a post-hoc analysis that looked for differential effects by gender.

[5] In view of the foregoing discussion concerning inadequate adjustment for confounding and inconsistency among studies, statements such as the following that appear on page 2-15, line 11 should be revised to acknowledge limitations and uncertainty: "Epidemiologic and toxicological evidence clearly demonstrates Pb-associated increases in behavioral problems, in particular, inattention and impulsivity (prior symptoms of ADHD)."

> "In the case of renal effects, causal inferences are limited by the potential for reverse causation, inconsistency in the epidemiological observations, and the absence of a demonstrable nephrotoxic mode of action at a blood Pb concentrations 5 µg/dL….Failure to temper conclusions with study design limitations was particularly problematic for the review of the renal effects of Pb."

These criticisms remain a major concern in the 2nd draft ISA. The summary section 2.6.3. "Renal Effects" essentially fails to acknowledge these limitations and concerns regarding the relevant literature. Chapter 5 addresses some of the concerns, albeit in a manner that would greatly benefit from a more balanced approach. Specifically, the new section, "5.5.2.5 Reverse Causality" appears to exist less as a critical analysis of the potential for reverse causation to explain (even partly) the inverse association of blood lead concentration and glomerular filtration rate, and more as a pointed attempt to refute its plausibility. This stands in contrast the comments on "reverse causation" put forth by authors of several key studies that have reported a significant BLL – GFR association. For example, in the discussion section of their longitudinal Normative Aging Study report on lead and serum creatinine, Kim et al (1996) state: "Our findings do not necessarily exclude the existence of an effect of impaired renal function on levels of blood lead. In line with epidemiologic and toxicologic evidence that low-level lead exposure causes subclinical impairment of renal function is the physiologically plausible possibility that decreased glomerular filtration or decreased tubular excretion results in decreased excretion of lead. Further research is required to test the hypothesis of a bidirectional relationship."

Unfortunately, the new section on "Reverse Causality" in the 2nd ISA offers no acknowledgement that such a bidirectional component remains an unanswered question. Similarly to the 1st draft ISA, the 2nd draft ISA dismisses the possibility of reverse causation in part by repeating the assertion that reverse causation is implausible because, "…the association was not limited to the segment of the population with potentially significant renal dysfunction in whom reduced Pb excretion would be more likely" (p 5-328). However, the 2nd ISA, like the first ISA, offers no citation or other substantiation for the supposition that there cannot be an inverse association between a filtered agent such as creatinine or lead and GFR in individuals whose creatinine or renal function falls within the "normal range". The narrative did respond to my comment in response to the 1st draft ISA that, "…steady state serum creatinine is inversely proportional to GFR, and in any person, decrements in GFR are associated with increases in serum creatinine even when the serum creatinine remains in the normal range." Two remaining points offered in section 5.5.2.5 to dismiss the possible contribution of reverse causation should be revisited. Two papers by Akesson et al (2005, 2006) were cited as finding no elevation of urinary lead in subjects with lower creatinine clearance. The narrative then argues, (line 17, page 5-328) "If reverse causality were the more likely hypothesis for these associations, lower creatinine clearance would be associated with lower urinary Pb, which it is not." The citation of the studies by Akesson et al (2005, 2006) in this context is puzzling, because in neither of these papers did the investigators either measure or report values for lead in urine. The second point offered in Section 5.2.2.5 is that neither blood lead nor chelated lead is elevated in patients with renal disease of known (i.e. non-lead related) cause. However, studies not cited in Section 5.2.2.5 (e.g Muntner et al, 2007 and others to be supplied) actually do show a trend of increased blood lead in subjects with renal failure.

The sections of Chapter 2 and Chapter 5 pertaining to renal endpoints assert several times that the literature is "consistent" in reporting a significant relationship between low blood lead levels and markers of kidney dysfunction (e.g page 2-20, line 5; page 5-307, line 9: "studies consistently demonstrate associations between higher blood Pb level and lower renal function in adults. The studies in this category provided critical evidence that the effects of Pb on the kidney occur at much lower doses than previously appreciated based on occupational exposure data"). On the contrary, as was pointed out in the CASAC consensus comments of December 2011, an inverse relationship between blood lead and glomerular filtration has *not* been consistently observed. For example, in the large general population study of de Burbure et al (2003) there was no significant association between blood lead and serum creatinine or other biomarkers of renal function in multivariable regression models. In the normative aging study (Tsai et al, 2004) there was no significant association between either blood lead or bone lead and serum creatinine in subjects without hypertension or diabetes. A further inconsistency arises from some studies of subjects with occupational lead exposure (Weaver et al, 2003a; Roels et al, 1994), in which higher blood lead was associated with improved renal function. Although, as noted in the comments supplied in the first CASAC report, this might conceivably be a consequence of lead-induced hyperfiltration, the actual cause has not been determined, and the unexplained inconsistency, which weakens causal inference, should be acknowledged. Instead, without justification, the 2nd draft ISA, (p 2-21), dismisses these "paradoxical" observations as reflecting unspecified "limitations of the study design." The observation by Evans et al, (2010) that individuals with low-level occupational lead exposure had a significantly decreased risk of developing renal insufficiency is another striking inconsistency. Evans and her co-author, C. Elinder, both of the Karolinska Instituet, wrote a review article in Kidney International in 2011 in which they contend that the available published literature does not allow the conclusion that low level lead exposure causes renal dysfunction. However, this important article was not cited in the 2nd draft ISA.

Finally, the observation in the first CASAC consensus comments that the absence of a discernible nephrotoxic mode of action of lead at low dose limits causal inference continues to lack acknowledgement in the 2nd draft ISA. Instead, contrary to the recommendation in the first CASAC report, the 2nd draft ISA continues to cite numerous studies of lead nephrotoxicity in animal models in which the lead dose greatly exceeded the much lower human exposure that is of interest with respect to NAAQS and the AQCD. For example, on p 5-304, the narrative describes an animal study in which exposure of rats to 100 ppm (≈100,000 µg Pb/L) of lead acetate in water for 14 weeks is characterized as

"low dose" exposure, when this exposure level is 4 to 5 orders of magnitude higher than typical human environmental lead exposure from water or diet.[6]

The sections of Chapter 2 and Chapter 5 in the 2nd draft ISA that discuss immunological effects of lead have been improved by partially responding to concerns expressed in the CASAC December 2011 report that certain studies were mischaracterized and that causal inference regarding some associations were overstated in light of shortcomings in the database. However, the conclusion expressed in the sentence, "Associations with asthma and allergy were observed after considering potential confounding by several factors, including, SES and allergen exposure" (page 2-21, line 22, and page 5-393, line 26) remains overstated, and should be revised. An appraisal of the epidemiological studies described in section 5.6.4.2 "Asthma and Allergy" would appear insufficient to infer a causal relationship. First, there is a vast literature on childhood asthma, an illness that has notably been increasing over the past 30 years contemporaneous with a dramatic decline in childhood lead exposure. Based upon the limited number of investigations (five) presented in table 5-29, it is apparent that only a handful of the numerous studies examining the etiology of childhood asthma and allergy have reported any positive association with lead exposure. Second, of the studies listed in Table 5-29, only one, by Pugh Smith and Nriagu (2011), reported a statistically significant association between blood lead (expressed as a categorical value BLL ≥ 10) and asthma after controlling for family income. The study by Joseph et al (2005) that adjusted (albeit indirectly and ecologically) for family income as a confounder did not observe a statistically significant association. The study by Jedrychowski et al (2011), which reported a significant odds ratio for a positive skin prick test based on cord blood lead but not contemporaneous blood lead in 5 year old children adjusted for maternal education, an incomplete surrogate for socioeconomic status. Overall, it is recommended that the epidemiological evidence relating lead exposure to childhood asthma and/or allergy best be regarded as limited and preliminary. The need for additional investigations of the relationship that carefully adjust for important confounders such as SES and allergen exposure should be acknowledged.

Section 5.7 contains an extensive discussion of the affects of lead on heme synthesis and red blood cell function. However, the following sentence appearing in the summary section on heme effects in Table 2-10, page 2-82 should be deleted because it overstates the overall evidence regarding any impact of a blood lead of ≈ 5 µg/dL on red cell function: "Associations were observed in populations with mean (or

[6] There are additional instances in which the sections of the ISA pertaining to renal effects appear not to have acknowledged comments offered in the CASAC report, even to the limited but still acceptable extent of disagreeing with them. The limitations of the studies of Yu et al (2004) and the related studies of Lin et al are not mentioned in the relatively lengthy discussion of these studies. On the contrary, without a detailed discussion of the major limitations of these studies, the 2nd draft ISA continues to favor the explanation that lead chelation has salutary effects on renal function in subjects with low level lead exposure. As noted in previous CASAC comments, EPA might prudently avoid offering an analysis of this controversial pharmacologic intervention in this document. The CASAC consensus comments recommended that "the practice of relying on extrapolation to characterize a dose-response relationship at a low blood Pb concentration (e.g., renal effects at a blood Pb concentration of 1 µg/dL in Figure 5-43) should be used sparingly, if at all, particularly when none of the studies included significant numbers of subjects with such a low blood Pb concentration, or when the validity of such extrapolation may be subject to considerable uncertainty. However, the 2nd draft ISA (p 5-343) continues to describe in the narrative the implicit adverse renal effect of an increase in blood lead from 1 to 10 µg/dL, even though it was derived from a study of older adult subjects who had higher blood lead concentrations earlier in life.

median) blood Pb concentrations as low as approximately 5 μg/dL." It appears that only one study referred to in the ISA examined the relationship of a blood lead concentration of ≈ 5 μg/dL on hematological parameters (Olivero-Verbel et a, 2007). This study was equivocal, because blood lead was positively correlated with rbc count, and nonsignificantly associated with hemoglobin. Moreover, the validity of the study findings was diminished by the fact that there was no control for nutritional factors including iron.

The December CASAC report (page A-5) recommended that the ISA offer a more detailed discussion of the relative contribution of different sources of lead to total contemporary lead absorption and blood lead concentrations. Although the presence of additional narrative on this topic at the bottom of page 4-6 in the 2nd draft ISA is welcome, it would be useful to include a graphical representation of this important data that attempts to partition sources of lead exposure (e.g. a pie-chart or related figure). It is interesting to note what seems to be a large contribution of lead from food and beverages (Table 4-1). In addition, the findings of Manton et al (2005) regarding the contribution of housedust to dietary lead might be worth mentioning.

The December CASAC report (bottom of page A-6) recommended that the section of the draft ISA pertaining to the rate of decline in blood lead following cessation of lead exposure be revised to reflect concerns that certain simulations utilizing the Leggett model depicted a more rapid decline in blood lead than is frequently observed empirically. The CASAC report took specific issue with the sentence on page 4-48, line 9 of the 1st external draft that stated, "Based on this hypothetical simulation, a blood Pb concentration measured 1 year following cessation of a period of increased Pb uptake would show little or no appreciable change from prior to the exposure event whereas, the body burden would remain elevated." Surprisingly, this identical sentence, which referred to cessation of lead exposure after an exposure period of 20 years, still appears in the same context in the second draft ISA on page 4-67, line 11. The criticism raised in the first CASAC report remains to be addressed. There has been insertion of language discussing alternative findings in the second paragraph on page 4-62 of the 2nd draft ISA. However, the presentation of different findings on different pages does not adequately clarify the issue.

The new section, 2.9.1 Public Health Significance, appropriately addresses the overall point that small outcome changes evident on a population basis (e.g. a few point shift in IQ, a few mmHg increase in blood pressure) may have limited clinical impact on any one individual yet nevertheless signify significant public health impact on the population as a whole. Several arguments in support of this are made, such as the significant impact of a shift in mean IQ on the tails of the IQ distribution. A few recommendations pertaining to this section are offered: 1) It might be noted that for some endpoints that have multiple causes and are subject to strong gene-environment interaction (such as blood pressure), a small change in the population mean may signify a relatively large change in some individuals, and no change in others. 2) The sentence on page 2-55, line 11 would benefit from revision for increased clarity; perhaps it could state: "Evan a small relative risk for an adverse health effect that is highly prevalent in a population can translate into large increase in the number of clinical cases." Similar revisions for increased clarity of this point are suggested for the narrative on page 2-56, lines 17- 28. 3) The discussion of the bell-shaped curve distribution of IQ at the bottom of page 2-55 should not be extended to "inattention", because unlike IQ, is not clearly established that the capacity for attention is

normally distributed. Here, and in the discussion that follows on page 2-56, the discussion of lead's affect on cognitive function is appropriate, but the inclusion of behavioral endpoints could prudently be removed because they are subject to more uncertainty.[7]

Overall, it is strongly recommended that the discussion about public health significance in this section focus predominantly, if not exclusively, on health endpoints such as cognitive function and blood pressure/cardiovascular disease, for which causation from environmental lead exposure has been established. Discussion of the public health impact of lead on endpoints such as behavior, renal dysfunction, asthma and allergy, and Alzheimer's disease, for which causal inference at low dose is subject to considerably more uncertainty, may detract from the strong point that can be made in this section with respect to cognition and cardiovascular disease.

The following sentence in Section 2.9, page 2-54, line 20 should be revised: "No *safe level* of Pb exposure has been identified in current or previous assessments and any threshold for Pb neurotoxicity would have to exist at distinctly lower levels than those associated with the lowest blood Pb concentrations examined in the epidemiologic studies included in this assessment" [emphasis added]. This appears to be the only sentence in the entire ISA where the term "safe level" was employed. It would be preferable and accurate to rephrase this sentence without use of the term "safe", instead noting that "No level of lead exposure has been shown to be without deleterious effect…" "Safe" represents a risk-management issue which is not the intended focus of this section.

The discussion in Section 2.9.2, Section 4.5.1 and Section 4.7.4 of the Air Lead – Blood Relationship appropriately notes that studies have reported a range of slopes and modeled relationships (e.g. log-log or linear). In its December 2011 report, the CASAC lead review panel suggested with respect to the discussion of this data (page A-8), "The narrative should consider offering a science-based judgment regarding which relationship(s) are optimal for quantitative risk assessment....The text that references the table should highlight the subset of studies that are particularly useful for the NAAQS evaluation and explain why they are useful. This approach would adhere to the goal of critically evaluating the literature and selecting key studies, rather than simply compiling study results." It does not appear that the 2nd review draft has adequately addressed this specific request regarding analysis of the studies that have examined the Air Lead – Blood Lead relationship.

Section 2.9.6.5 Race and Ethnicity (and Section 6.3.6) do not sufficiently discuss the potential susceptibility of African-Americans to lead possibly arising from factors not mediated by SES or exposure. For example, the document does not discuss the important recent article by Theppeang et al [American Journal of Public Health. 98(7):1248-55, 2008] that found that African Americans have

[7] On page 2.56, line 5, the following statement should be revised: "In cohorts of children where Pb-associated decrements in cognition and attention were observed, lower academic performance, antisocial behavior, or delinquent behavior assessed in adolescence or in early adulthood were also observed in association with blood Pb levels." As noted above, a distinction between academic performance and delinquent behavior as endpoints is indicated. While both has been observed in some cohorts (notably the Cincinnati cohort studied by Wright and Dietrich and colleagues [2008]), increased delinquency has not been reported in other cohorts in which cognitive effects have been found, such as the Boston prospective cohort studied by Bellinger and colleagues.

higher bone lead, after controlling for SES related variables. The document does not address other articles that have found black children to have higher BLL after controlling for SES. It has been suggested that genetic differences in calcium metabolism may contribute to higher lead stores in blacks. Moreover, the document fails to note important earlier literature that has suggested that blacks may be at higher risk of lead associated increases in blood pressure than nonblacks, e.g. (Vupputuri S, He J, Muntner P, et al. Blood lead level is associated with elevated blood pressure in blacks. Hypertension 2003;41:463–8; Sharp DS, Benowitz NL, Osterloh JD, et al. Influence of race, tobacco use, and caffeine use on the relation between blood pressure and blood lead concentration. Am J Epidemiol 1990;131:845–54) However, this lead-race interaction has not been consistently observed, e.g. Martin et al. Am J Epid 163:467-478; 2006).

Portions of the discussion of lead chelation in Section 5.3.2.3 (page 5-99) are misleading and subject to serious misinterpretation, particularly as they pertain to the studies of Stangle et al, 2007 and Beaudin et al, 2007. The following sentences on page 5-100 are misleading and require clarification and revision: "In summary, succimer or chelation treatment appears to be able to restore Pb-dependent impairments of learning and arousal and be neuroprotective in a concentration-dependent fashion. In these studies, succimer use was more efficacious at *lower doses of Pb exposure*" [emphasis added]. First and foremost, the ISA's description of lead chelation in the studies by Stangle et al and Beaudin et al (both of which utilized the same study design) fails to explain that these studies examined only two lead dosing groups: a medium lead dose that produced a peak blood lead prior to chelation of 40 to 60 µg/dL, and a high lead dose that yielded a peak blood lead of 100 to 140 µg/dL (cf Beaudin et al, 2007, page 190). Second, the use of succimer in the control rats, which had blood lead concentrations of approximately 1.5 µg/dL, produced deficits in cognitive function and behavior that were of the same magnitude of high lead exposure alone. It is important to include this additional information in the narrative, lest it be misinterpreted by some as supporting the value of lead chelation in children with low level environmental lead exposure and low blood lead concentrations.

Additional comments and recommendations:

Page 2-14, line 8 (and the corresponding sentence elsewhere): Please reconsider the statement: "The concentration of Pb in urine follows blood Pb concentration, in that it mainly reflects the exposure history of the previous few months and therefore, is likely a relatively poor index of Pb body burden." Urine lead more closely follows plasma lead than it does whole blood lead, and it changes more rapidly and frequently in response to changes in exposure than does blood lead. Rather than reflecting lead exposure in the past few months, urine lead is more a reflection of lead exposure within the past few days. Urine lead responds more quickly to changes in external lead exposure than does blood lead (cf. Gulson B et al, Blood Lead–Urine Lead Relationships in Adults and Children, Environ Res A 78:152-160; 1998).

Page 2-25, line 23: The first sentence of this paragraph requires revision for clarity.

Section 2.8.1. "Modes of Action Relevant to Downstream Health and Ecological Effects" is a well-written summary.

Page 2-58, Table 2-6: The fourth row appears to have an erroneous entry that should be checked: "Creatinine ≥ 30 mg/g creatinine indicates albuminuria" [sic]

Page 2-70, line 7: The following sentence appears too general and should be revised: "Studies that found associations with concurrent blood Pb levels also tended to find associations with prenatal cord or maternal blood Pb levels." In some longterm prospective cohort studies of lead and IQ, e.g. the Boston cohort studied by Bellinger and colleagues, the Port Pirie cohort reported by Tong et al (1996), and the pooled analysis by Lanphear, the influence of cord blood lead on IQ in late childhood was not significant. Conversely, the Mexico City Prospective study reported by Schnaas et al found only prenatal BLL to be predictive of later childhood IQ. The Yugoslavia cohorts studied by Wasserman and colleagues found concurrent effects of both prenatal and postnatal blood lead.

Section 2.9.6.7 Proximity to Pb Sources and Residential Factors, and the related sections of Chapter 6 should note that residential water service lines made of lead are a risk factor for elevated childhood BLL (Brown MJ et al. Environ Res 111:67-74; 2011).

Section 2.9.6.1 Co-exposure of Lead with Metals and Chemicals. On page 2-78, line 22, the sentence regarding the impact of As on Pb bioavailability should be checked, as a review of the cited reference in Section 6.1 (Wang and Fowler, 2008) does not appear to support this contention. On page 2-78 line 29, the following sentence appears to be speculative and should be deleted:
"Since Pb is acid soluble, fluoridation may increase Pb concentration in water through leaching from pipes and Pb solder (Section 4.1.3.3)." In the ISA, this sentence appears to be entirely based on a single *in vitro* study by Maas et al (2006) examining the impact of fluoride on lead leaching from brass fixtures. This article did not address lead from pipes or solder. This statement should be eliminated in the absence of any other data indicating that fluoridation increases the risk of lead exposure or elevates blood lead concentrations. Alternatively, if studies of adequate quality do address the relationship between fluoridation and lead in drinking water, the topic should be more critically and thoroughly addressed.

Dr. Roman Lanno

Comments on Chapter 7

The causal statements for ecological effects discussed in Chapter 7 have been re-evaluated as advised by CASAC. There are now separate causal determinations for terrestrial and aquatic biota for each endpoint under consideration. In addition, the chapter now incorporates additional findings from the 2006 Pb AQCD on the effects of Pb on ecosystem receptors, an enhanced discussion of bioavailability and bioaccessibility, and separate discussions of marine and freshwater toxicity in the aquatic ecosystem section.

Please comment on the adequacy of these various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information.

Chapter 7 has been greatly improved with the addition of very good introductions to sections and also by providing background reference to previous AQCD documents and concise summaries of sections where appropriate. The US EPA has provided a complete coverage of the more recent additions to the knowledge of Pb exposure, toxicity, and effects to ecological receptors in terrestrial, freshwater, and marine ecosystems.

Although the revised ISA contains much new information presented in an organized manner, the information is not summarized and integrated into a meaningful synthesis. Summary tables listing media-based exposure concentrations (soil, freshwater, marine; nominal or measured) with their respective responses and key abiotic modifying factors (e.g., pH, organic carbon, cation-exchange capacity (soils), water hardness, etc.) would help in further organizing the data to facilitate a synthesis. Detailed tables could be provided in an Appendix (e.g., as in the 2006 Pb AQCD) with summary tables of the most relevant data presented in the text of the ISA to guide discussion.

An initial discussion should include the relevance of studies where responses were observed at very high Pb levels that may not be expected in most environmental scenarios. In a similar manner, studies where organisms were exposed to Pb at very low levels should also be carefully scrutinized as to the validity of the studies (i.e., were Pb concentrations nominal or measured, did they approach detection limits). Finally, studies where Pb exposures overlap actual expected environmental levels of Pb (see Table 2-1) would comprise the main focus of the discussions.

Although some discussion of bioavailability is provided, integration of this concept into the discussion of Pb effects (e.g., how water quality parameters affect Pb toxicity) observed in different media should be attempted.

In the section on terrestrial toxicity tests, there are a number of paragraphs that refer to tests conducted with plants in hydroponic systems. A clear distinction should be made between tests in hydroponic solution and tests conducted in soil. There are physiological differences between plants in hydroponic

systems (e.g., reduced development of root hairs) and plants exposed in soils that make comparisons of toxicity between these exposure systems difficult and extrapolation from hydroponic systems to soils systems problematic. A similar situation arises when discussing nematode tests that are apparently conducted in agar or some other test medium with exposure concentrations reported in ug/L for soil organisms. It would be important to note when toxicity tests are not conducted in actual soils and stress that the comparison and extrapolation of this data to toxicity tests in real soils should be done with extreme caution.

Throughout Chapter 7, it is often not clear when exposure doses are expressed as nominal or measured concentrations. When round numbers (e.g., 100, 250, 5, 30 mg/L or mg/kg) are presented, I assume that these are nominal concentrations. Often times it is stated that these are nominal concentrations, which is excellent. However, if measured concentrations are available, these should be reported in lieu of nominal concentrations. If only nominal concentrations are provided in the original research, then these studies should be considered as secondary data and so noted since one of the major criteria for primary data is actual measured exposure concentrations.

There are a number of paragraphs in the terrestrial section where Pb exposure concentrations are presented but little information is provided regarding the physical and chemical characteristics of soil that have the potential to modify Pb toxicity. Reporting this information would provide some means of comparison of the effects of modifying factors of toxicity (see previous comment on bioavailability).

There are a number of paragraphs where the reporting of exposure doses are in different units (e.g., ug/L and mg/L) where standardizing the expression of dose would greatly facilitate the comparison of toxicity, both within a study and amongst different studies.

Dr. Richard L. Poirot

Overall, **Chapter 3** is much improved, with changes responsive to previous review comments. The discussion of historical changes to emissions inventories is much more clearly presented. The expanded discussions on natural and intercontinental background Pb and on air Pb/ soil/Pb relationships are helpful. The HERO system works flawlessly and represents a major improvement to the review process.

I was disappointed that the comparison of collocated Pb measurements in different size fractions was removed (rather than repaired – to include only concurrent, above-MDL, paired samples), as I think there could be useful information content there. At a minimum, you might just append the Cavender & Schmidt (2007) memo comparing Pb in different PM sizes prepared for the previous NAAQS review, although hopefully this might be updated to include a few more years of data. You could also reproduce the similar (table 3) information in the excellent Cho *et al.* (2011) literature review paper. Possibly you could also summarize the size distribution results derived from the many studies you cite (and several others listed below) using MOUDI samplers in a single table or graphic. Of particular interest would be information about how Pb particle size distributions might change over time, by season, by proximity to different source types, or as a function of concentration or chemical composition. It would also be helpful if information on particle size, concentration and/or composition presented in Chapter 3 could be more directly linked to the exposure and toxicokinetics information in Chapter 4.

The discussion of limitations of the current TSP FRM sampler has been much improved, and various other Pb sampling (& analytical) methods are reviewed. However, there isn't really much discussion of practical alternatives, such as the louvered lo-vol inlet - or scaled-up version of it (Kenny et al., 2005), other than to indicate they "could be tested". There is also no discussion, in chapter 3 or 4, relating to what particle cut size(s) would be most desirable in a Pb FRM. The "Integrative Summary" states (p 2-6) that "the Pb-TSP indicator was retained in 2008 in recognition of the role of all PM sizes in ambient air Pb exposures", but relatively little information is presented (in Chapter 4 or elsewhere) on what the role(s) of different Pb particle sizes actually are in terms of human exposure and uptake. Arguably inhalation (fine particle only) is more efficient than ingestion (Hodgkins *et al.*, 1991); ingested fine particles are absorbed more efficiently than coarse ones (Barltrop and Meek, 1979); and are composed of more inherently soluble Pb compounds than coarse particles. Fine particles penetrate more efficiently into indoor environments – by various transfer mechanisms, and once deposited to surfaces, are more readily picked up and ingested (Juhasz *et al*., 2011). So arguably, a sampler (like the TSP hi-vol) that excludes progressively larger fractions of progressively larger particles (and does so most effectively when high wind speeds suspend the highest concentrations of ultra-coarse particles) – may not be so bad after all…

Chapter 3 concludes that our understanding of TSP sampling errors, particle size distributions, and possible alternative samplers has not changed much since the last review cycle. This is true enough, but unless we plan to hear similar laments in each subsequent Pb NAAQS review cycle, we need to start thinking more proactively about alternative sampling approaches. What are the desired particle cut size characteristics for sampling Pb in the ambient air? If a sampler could be developed that would

consistently capture particles larger (or smaller) than those captured by the hi-vol under different wind conditions, would that be an improvement? Are there practical upper particle cut size limits to what can be consistently achieved for different wind conditions by filter sampling techniques, and might these size limits also be justified by the spatial (population) representativeness of the resulting measurements, and/or by the decreasing bio-relevance of larger particle sizes? Is there a need to start routinely collecting additional information on particle size distributions at sites with high Pb concentrations?

Specific Comments

P 3-1, lines 25-26: Maybe insert "a majority of" before "ambient airborne lead", as you indicate on p 3-8 that organic Pb – which may comprise up to 20% of Pb emitted from piston aircraft - would remain largely in vapor phase.

P 3-5, lines 4-5: It's not clear what "this category" refers to. Should there be some preceding statement indicating what (relatively large) % of Pb was emitted from what (relatively small) % of the largest emitting counties? Along similar lines, it might be helpful to include something like a list of the largest point sources, at least summarized by category, if not by name. Given that there are 20,000 airports contributing to the largest total emission category (with roughly half the Pb emitted at/near the airport), it's hard to get a sense of how individual airports compare with other large Pb sources.

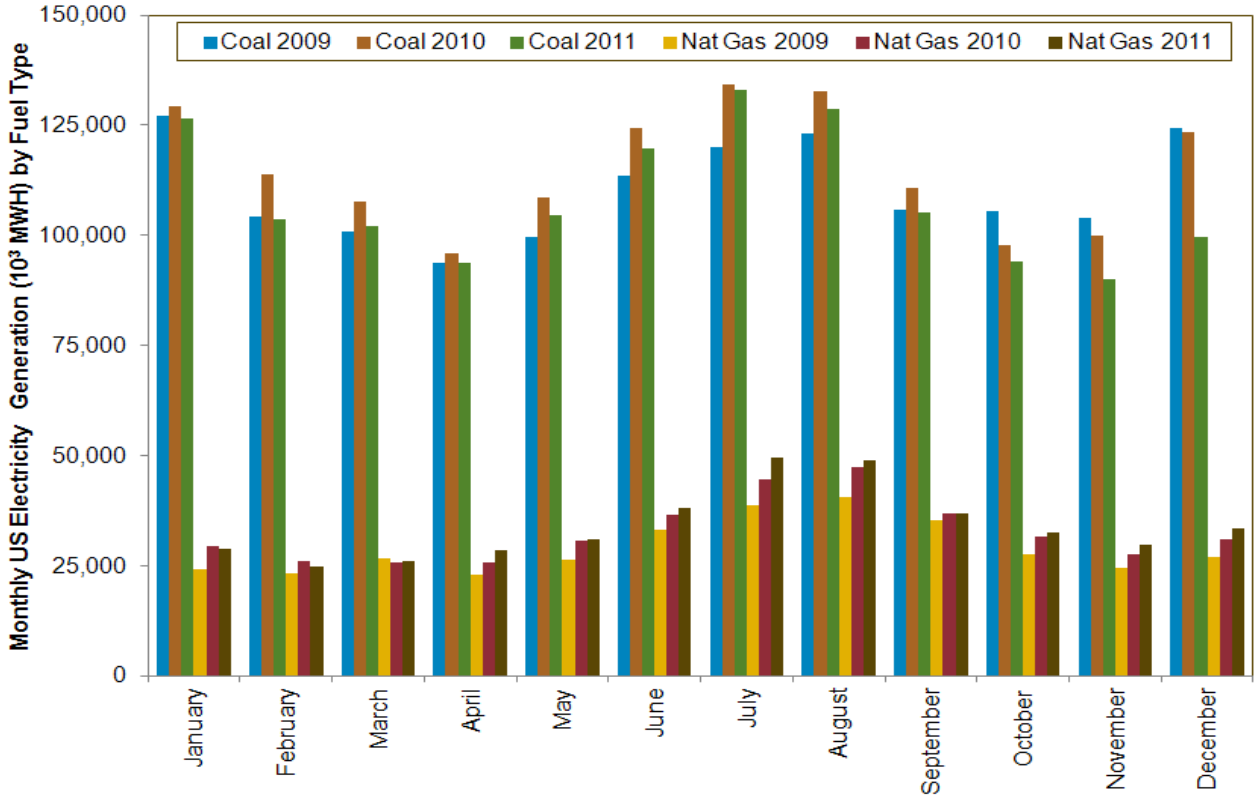
P 3-9, line 2: Can you indicate how far downwind of the smelter the concentrations were 35 x higher? It's also not clear what "(0.625-0.880 $\mu g/m^3$)" refers to. I assume it might be the range of measured downwind concentrations. If so, you might move it to follow "downwind" – rather than "upwind".

P 3-9, lines 20-21: I assume this estimate of "nationwide median fugitive emissions" is specific to secondary Pb processing facilities? Also, in this section you use the terms "secondary", "smelting", "processing" and "recovery". Do these have different meanings? If so, some explanation would help.

P 3-10, line 11: Is there any indication of what fraction of Pb from coal combustion is in the form of relatively insoluble $PbSO_4$? See for example Tan *et al.* (2006), Xie *et al*. (2009).

P 3-10, lines 15-19: I wasn't aware that such large amounts of crude oil (Pb emissions similar to residual oil) were being burned. Also, adding these estimates for coal (200 tons/yr), crude (100-500 tons/yr), and residual oil (25-700 tons/yr), yields a range of 325 to 1400 tons/yr. This is a large range and a factor of 2 to 10 greater than the 149 tons from fuel combustion presented in Figure 3-3. Are emissions estimates really this uncertain, and if so (or if not) some additional discussion seems warranted.

P 3-11, lines 16-18: Just citing West Virginia patterns for US seems simplistic. I think there's generally a summer peak in US power demand due to air conditioning, but the summer peak in utility coal burning is not much higher than a secondary winter peak, as much of the increased summer power demand is supplied by seasonally cheap natural gas.



From: http://www.eia.gov/electricity/monthly/epm_table_grapher.cfm?t=epmt_1_2

P 3-11, lines 21-22: Maybe mention that this 63% Pb from incinerators was based on just 6 sample days.

P 3-12, lines 17-20: Again, it seems worth mentioning that this 20% Pb from Canadian wildfires was out of 6 days, 1 or 2 of which included the highest wildfire smoke concentrations ever seen in that region.

P 3-14, line 12: This higher concentration of Pb in the 0.18 to 0.32 µm size mode does not seem consistent with ground-up wheel weights (i.e. it's not the fine tail of the coarse mode). Can you offer other explanations, or at least observe that there may be other roadway (or regional) sources of fine mode Pb? See for example Thorpe and Harrison (2008), Maher et al. (2008).

P 3-16, line 14: Maybe change "comparison" to "difference".

P 3-16, lines 30-31: It's not clear what these percentages refer to. A month after demolition, was Pb 18% higher, 18% higher and 29% higher in dust on alleys, sidewalks and roadways than it was in those locations prior to demolition?
P 3-21, line 4: You might add something like "and systematic reductions in emissions from other lead sources" after "motor vehicles". Over the past 20 years, most of the Pb emissions reductions and air improvements have come from non-MV sources.

P 3-21, lines 8-12: [Seems like this paragraph belongs in section 3.3.1.2 (Deposition)]. I also think you overstate the solubility argument. Particle size dynamics are a more important contributing factor to the different removal mechanisms than solubility. Large particles will dry deposit relatively quickly whether they are soluble or not, nor would they tend to be removed predominantly by wet deposition processes if they were more soluble. For example, the current GEOS-CHEM treatment of (soluble) sea salt aerosol deposits ¾ of small particles (<4μ) by wet deposition, and ¾ of large particles (>4μ) by dry deposition. (http://wiki.seas.harvard.edu/geos-chem/index.php/Sea_salt_aerosols).

Fine particles do not dry deposit efficiently in any case, and insoluble components of fine particles are often coated/mixed with soluble species in internally mixed aerosols, and readily removed by wet deposition processes. Freshly emitted (fine particle) black carbon, for example, is considered primarily hydrophobic, but ages over time, becomes mixed with soluble species, becomes hydrophilic, and is removed primarily by wet deposition (Reimer *et al.*, 2010). An average of 47% of Pb in 2005 and 2006 wet deposition samples in the eastern Mediterranean was insoluble (Theodosi *et al.*, 2010). This paper also includes interesting observations of seasonal patterns in wet & dry Pb deposition, and changes in solubility with precipitation pH.

P 3-24, lines 3-6: You could change "at" to "near" in line 3, as the upper bound Pb V_d reported in the 2006 CD was 1.3 cm/s. Also, the 12-17 mg/m^2-year dry Pb deposition reported here for Tokyo Bay was not more than 10 times the upper bound of the range reported in the 2006 CD - which included 8.4-14 mg/m^2-year dry Pb deposition reported by Yi *et al.*, (2001) near Lake Michigan for 1993-1995 (see p. 2-57 of the 2006 CD).

P 3-24, line 32: You could change "in locations near" to "at" or "from".

P 3-25, lines 6-11: I don't understand why a "smoothed" gradient indicates resuspension. With no resuspension, I would still expect a relatively smooth gradient in deposition of pollutants away from long-term emission sources – maybe declining with the log of distance from source. More detail is needed to explain this. Also, any spatial pattern of lead in soil would likely reflect historical air concentrations and sources (including resuspension), rather than influence from current sources.

P 3-28, lines 29-31: These measurements indicating relatively greater resuspension of fine Pb than coarse are an interesting contrast with the model estimates of relatively greater suspension of coarse than fine particles on preceding page (p 3-27, lines 11-19).

P 3-39, lines 11-12: Is this (1 μg/l) the concentration of Pb (rather than DOC or Fe)?

P 3-46, line 17: What is "high quality deciduous litter"?

P 3-47, lines 32-37: You first refer to what Perdrial *et al*. "postulated", but then refer to it as "important new evidence".
P 3-53, lines 23-24: This sentence needs work.

P 3-56, line 14: In discussing the TSP FRM sampling biases with wind speed, it might also be worth noting that the lower collection efficiencies for larger particles at higher wind speeds coincide with (windy) conditions most conducive to suspending large Pb containing particles and sustaining their atmospheric presence over longer times and distances. Conversely, on days when samplers are not running, the TSP FRMs are also susceptible to passive sampling artifacts, increasing with increasing wind speed and particle size (McFarland *et al.,* 1979).

P 3-57, lines 6-7: "…have been thoroughly reviewed" (20 years ago). It would be helpful somewhere to include some discussion of what particle size(s) it would be desirable to collect (are most relevant to human exposure). Here or in Chapter 4, some discussion of how particle size characteristics relate to Pb uptake would be helpful, along with a more proactive demonstration that coarse particle Pb – within some size limits - is, in fact, of equal importance as fine Pb. How would we expect a given Blood Pb: Air Pb ratio to shift, if the size distribution of Air Pb particles shifted to larger (or smaller) particles?

P 3-57, line 29: Don't you mean "low-volume" PM_{10}?

p. 3-85, lines 4-5: While Pb compounds in PM may have relatively high densities, particle size is typically a more important factor, and it's only the larger particles (regardless of their densities – within limits) that tend to settle out quickly. Pb incorporated in small particles tends to be combined with other (lower-density) compounds and/or is not efficiently deposited near its emission sources – hence the wide spatial distribution of historical automotive Pb in remote locations.

P 3-86, line 6: Could you give an example of what you mean by high spatial variability? It might be helpful to put this in context by comparing to the spatial variability of other pollutants.

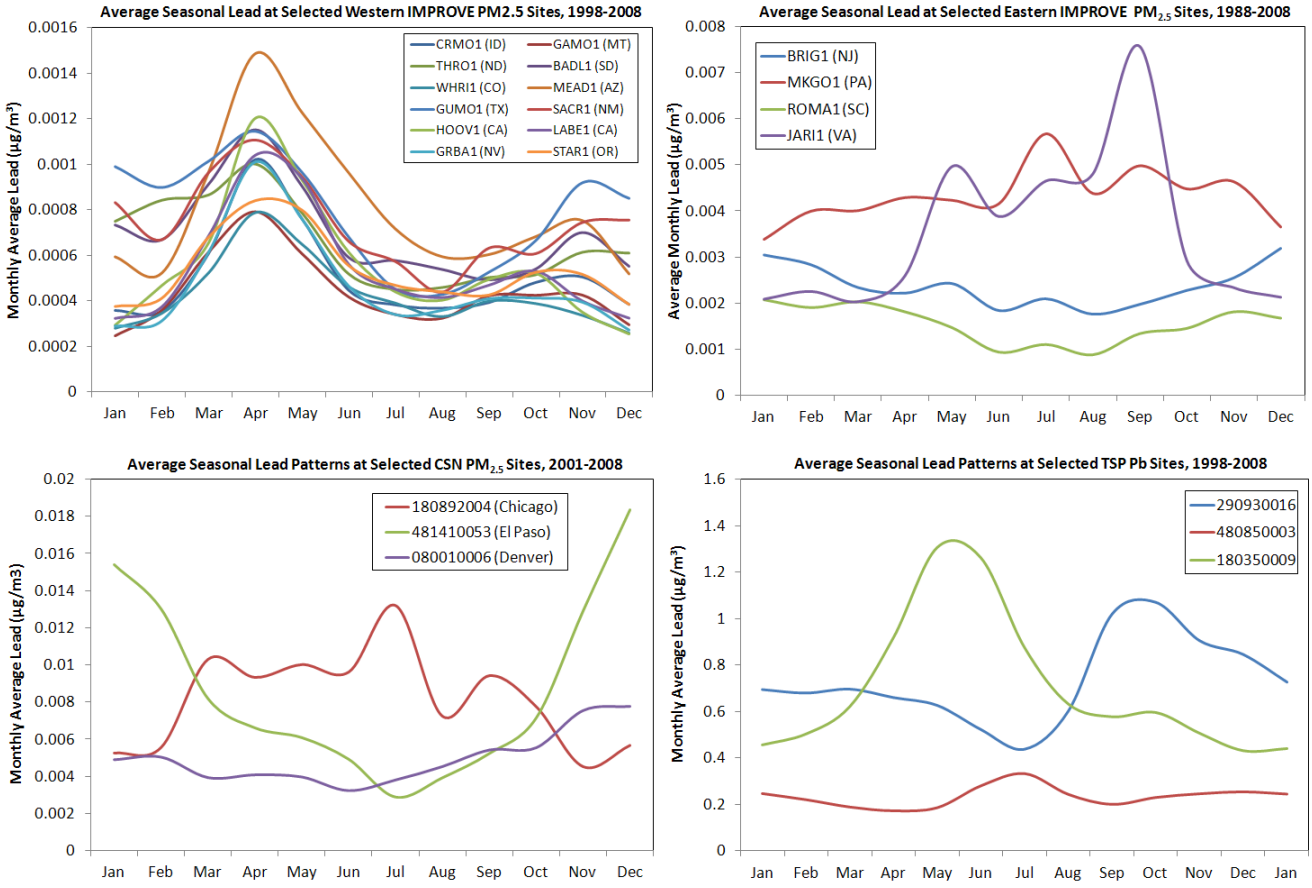
P 3-85, line 36: Add "m" after "2".

P 3-88, Figure 3-20: This is a good example. It might be useful to have some other graphical depictions of long-term Pb trends to help support the emission inventory trends - for example: http://www.epa.gov/airtrends/lead.html .

P 3-93-96: There appears to be very little seasonal variability in the ambient Pb data as summarized here (hard to see any), and only very slight summer peaks in some of the Appendix 3.8.1 tables. This seems inconsistent with various recent analyses of Mielke, Laidlaw and others suggesting summer (or dry season) peaks in both fine soil and Pb. There do seem to be relatively strong seasonal peaks in children's blood lead in many studies. While several of these are mentioned in Chapter 4, there's not much associated discussion of potential causal or contributing factors. Other older and newer studies that

might be considered include: Baghurst *et al*., 1992; US EPA, 1996; Yiin *et al*., 2000; Kemp *et al*., 2007; Havlena *et al*., 2009; Mielke *et al*., 2011; Laidlaw *et al*., 2011a, b). It might be useful to include some discussion of similarities & differences in seasonal patterns of air Pb and blood Pb, along with explanations of mechanisms that may contribute to the seasonal blood Pb increases.

I also think the aggregated summary nature of Figures 3-24 through 3-26 may be masking some of the unique seasonal patterns at individual sites – that may be revealing of source influences, or may affect exposure patterns. Note for example, the (low concentration but) distinct April peak in $PM_{2.5}$ Pb at remote Western IMPROVE sites, which would be consistent with Asian transport (van Donkelaar et al., 2008; Ewing et al. 2010, DePaolo, 2011). Note also the different seasonal patterns in other rural & urban $PM_{2.5}$ sites and at selected source-oriented TSP sites.



P 3-96, lines 10-16: You could add a category where Pb is mainly <2.5 µm – as would be expected from piston engine aircraft and other fuel combustion sources.

p. 3-97, line 2: You could add "TSP" before "sampling".

P 3-97, line 24 – and on following few pages: I note that you cite partial results from 7 or so different studies that all employed MOUDI samplers. What about summarizing all the MOUDI results in a single table or graphic to give an indication of similarities & differences in the particle size distributions observed in these different studies from different locations – possibly adding a few others like Albuquerque *et al*. (2012), Csavina *et al*. (2011), Fang and Huang (2011), Gao (2009), Lin *et al*. (2005), Wang *et al.* (2005), etc.

P 3-99, lines 33-37: You indicate that Pb and As were highly correlated in PM_{10} samples. It would be helpful to know if Pb:As correlations were lower in the fine and ultrafine samples from Hays *et al*. (2011), as this could help support (or not) the wheel weight hypothesis.

P 3-100, line 5: Do you mean "ng/m^3"?

P 3-100, line12: How "low"?

P 3-100, lines 22-24: How do the east & west directions relate to sampler orientation to the roadway, and is there any indication of roadway influence – in the larger or smaller size fractions? Possibly the review of this study could be deleted here as it's repeated in more detail in the following section – and is more relevant to the "non-road influences at near-road sites" theme of that section.

P 3-100: Another possibly useful reference on roadway Pb influences on air & soil Pb, vertical soil profiles and bioavailability is Preciado and Li (2006). Maher *et al*. (2008) present recent evidence of vehicle exhaust fine particle Pb deposition on leaves of roadside trees. Several more recent publications by Mark Laidlaw (2011a, b) make a persuasive case for the importance of resuspended roadside soils. See also his extensive bibliography at http://www.urbanleadpoisoning.com .

P 3-104, lines 10-11: Could you give an explanation for the large decrease in collocated sites – from 129 in 2007-08 to only 16 in 2009. Intuitively one would expect an increase in sites with the tighter new 2008 Pb NAAQS.

P 3-104, Figures 3-28 & 3-29: I'm suspicious about the several perfect 1.0 correlations between Pb and SO_2, $PM_{2.5}$ and CO in figure 3-28. Do all the "source" and "non-source" categories in these figures refer to the associated pollutants or to the Pb (or both)? I would imagine it might be possible to have a source-oriented PM_{10} site where collocated Pb measurements were not considered source-specific. What would be a "source" site for ozone?

P 3-105, line 32: So what's the implication of the Pb-humate observation?

P 3-107, Table 3-10: Considering $PM_{2.5}$ is included in PM_{10}, and PM_{10} in TSP, some of the numbers and huge differences in correlations for the different size fractions look very suspicious. For example the correlation between Pb and Fe is 0.43 for TSP, 0.99 for PM_{10} and -0.51 for $PM_{2.5}$. For Pb vs. Ni the correlations are 0.08 for TSP, 0.99 for PM_{10} and -0.67 for $PM_{2.5}$. I don't believe it, and suggest double-checking these numbers and either find a way to explain, comment critically, or delete the reference.

P 3-108, Figure 3-30: I like this figure! It might be instructive to show something similar for IMPROVE data. Also, some discussion of the relatively high correlation between Pb and K seems warranted. K is often a good tracer for wood smoke, although fireworks are also a large but only occasional source, and K is also contributed by soil and sea spray. None of the above – with the possible exception of woodsmoke (from forest fires) has been suggested as an important Pb source.

P 3-109, lines 23-25: Needs work.

P 3-110, line 1: Add "Pb" before "concentrations".

P 3-110, lines 7-14: The seasonal patterns of Pb at many remote western US IMPROVE sites show a distinct (but very low concentration) Spring peak, which would be consistent with Asian transport. See figure below p 3-106 comment.

P 3-112, line 1: I think you mean "contemporary", not "contemporaneous".

P 3-112, line 23: Is "debrided" the right word here? Maybe peeling, degrading, flaking…

P 3-113 and generally: It's helpful to include sample depths when you report soil concentrations, which you do in some cases but not in others.

P 3-113, lines 27-30: This indication of declining Pb concentrations in soils (is the only one discussed here but) could be an important point suggesting that current Pb loading rates are insufficient to sustain Pb concentrations at locations where resuspension of historically deposited Pb may be important. See also the roadside soil Pb profiles in Preciado and Li (2006), which show highest Pb concentrations at depths of 0.25 to 0.3 meters, decreasing substantially toward the surface.

P 3-114, lines 29-30: As indicated previously, some explanation would help understand why smooth gradients imply resuspension.

P 3-117, line 28: Add "g" after "μ".

P 3-118: At some point in this section (or elsewhere), it would be helpful to discuss mechanisms like resuspension and air movement vs. tracking on shoes, etc. by which soil Pb gets incorporated into indoor dust (Layton and Beamer, 2009). Any information on the influence of particle size on these transport mechanisms would be helpful.

P 3-122 & 3-123, Figures 3-33 and 3-34: I don't understand these figures and think additional explanation is needed. Why is the 1992-94 pattern - showing a large increase at Atlanta with declining concentrations downstream - so different from the closely overlapping 1990-1995 sediment pattern which shows no increase at Atlanta for that period or for any other time period back to 1975? Is this just because in the samples used to construct Figure 3-34, there were no samples near Atlanta (about 650 miles upstream) until you get to about 500 miles downstream? If this is the case, the lines between the 2

right-hand points are likely misleading as they suggest gradual increase from 750 to 500 miles, when in fact we expect a large step up at 650 miles, followed by gradual decline downstream. Adding further confusion, it looks like the largest concentrations in 3-34 at 500 miles occur where the Pb background (shown only in 3-33 but included in the 3-34 caption) jumps up.

P 3-123, lines 10 & 13: Could you report the MDL?

P 3-124, lines 11-18: This paragraph seems unnecessary – or could be shortened to "There are no routine measurements of Pb in precipitation in the US."

p 3-125, line 15: I don't think "the greatest reductions occurred in late 1990s" is really correct for either Europe or the US. In the US, I would think the greatest reductions in Pb emissions, air & deposition likely occurred in the late 1970s and early 1980s (see Figures 3-1 & 3-20). Maybe you could say something like "prior to 1990, with relatively smaller reductions in recent years". As indicated above, some graphic illustrations showing long-term decreases in air Pb would be helpful.

P 3-129, line 75 (& Fig 3-37): A possible explanation for this extreme value at Noatack could be fugitive emissions from (or similar bedrock ore deposits to) the relatively nearby Red Dog mine (one of the largest Zn & Pb mines in the world). See: http://www.reddogseis.com , Hasselbach *et al*. 2005, and http://dec.alaska.gov/air/reddog.htm.

P 3-139, lines 8-18: As indicated in comment on p 3-29, I think you overstate the importance of solubility. Also, if coarse Pb is predominantly insoluble, then presumably it's less readily adsorbed when ingested, and may be relatively less injurious than its (soluble, respirable) fine particle counterparts.

P 3-139, line 21: You might add "most" before "surface waters". Surely there are some where current or past mining or smelting operations or other sources are locally more important than atmospheric deposition (for example Kurkjian *et al*. 2004; EPA Region 9 (2012); Coeur Alaska, inc. v. Southeast Alaska Conservation Council). While it seems logical that atmospheric deposition has been the most important source of Pb input to most surface waters historically, I wonder how current Pb deposition rates compare to resuspension from sediments (p 3-140, lines 1-3), or urban runoff contaminated by Pb wheel weights, historically deposited Pb, etc.? For example Davis *et al*. (2001) estimated that wet and dry Pb deposition contributed less than 20% of total Pb loading in urban runoff.

P 3-140, lines 26: This may be true, although it seems like you haven't tried very hard. You could have included some discussion of the excellent Cho *et al*. (2011) review paper, included a more carefully conducted update of the comparison of Pb in different size fractions included in the last draft Pb ISA (but dropped here), summarized the results from the various (at least 7) MOUDI studies you list here, and added a few others such as Albuquerque *et al*. (2012), Csavina *et al*. (2011), Fang and Huang (2011), Gao (2009), Lin *et al*. (2005) Wang *et al*. (2005), etc.

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Dr. Joel G. Pounds

Comments on Chapter 4

Comments on accuracy of the interpretation of the science:

In general, the literature results presented in Section 4.1 (dietary lead exposure) is clearly written and faithfully presented. However, the text of individual paragraphs provide little interpretation, context, or summary. That is data are merely presented without evaluation, thus the reader must guess the importance and impact of the reviewed data to the ISA. For example, the point of paragraph beginning on P4-20-L12 is unclear without inclusion of a summary sentence that helps the reader understand why these two studies were reviewed. The paragraph identifies an "important problem" but does not convince the reader as to the importance of the problem or the insights offered by the reviewed studies. In contrast, most paragraphs of 4.2 are summarized with an evaluative sentence that places the reviewed data in context of the ISA.

Are uncertainties and limitations of relevant data, methodologies and approaches adequately discussed:

P4-30-L-23.

P4-33. Organic Lead Section. Suggest ISA include sentence or two that summarizes the importance, or lack thereof, of organic lead compounds to the lead body burden or blood lead.

P4-50, L3. Very nice paraphagrh describing uses and limitations of mechanistic models. P4-100 is a parallel nice paragraph describing the use and limitations of empirical models.

I have several comments related to blood Pb simulations P4-48; P4-8, 4-9, 4-11; and other figures and text. The ISA authors are commended for their efforts to provide lucid simulations that collectively illustrate relationships between blood Pb and selected tissue. These simulations are very helpful to provide an interpretative context for blood lead and bone lead measurements in human individuals and populations.

1. It would be helpful to include a little more information in the "Note" for each simulation. For example, how much lead was "administered"? When Pb administration to the model was changed, was input set to zero Pb or some baseline?

2. I'm unclear why "time-averaging" of urine Pb, blood Pb etc. was used in many of the Figures in this Section. I think of time-averaging as a method to decrease variability of experimental in addition to experimental error. However, the simulations have no variability in this sense. Over what time scale are

the data averaged? The time-averaged data could be more useful if compared and contrasted with experimental data, yet this comparison is not provided.

Specific recommendations to refine interpretation / representation of the science:

P4-30-L24-28. The text states "If properly measured (e.g. time-integrated blood Pb), under most conditions Pb bioavailability is equivalent (or nearly equivalent) to Pb absorption". This statement seems conceptually incorrect. Agreed, blood lead is the central compartment of biological reality and the models that describe these biological processes. However, blood lead also includes inputs from soft tissues and bone. Thus, time-integrated blood lead will over-estimate Pb bioavailability/absorption.

P4-34-35→ The role of "nutritional deficiencies" in lead metabolism is more complex than summarized here. The papers reviewed are interpreted correctly but the review is necessarily superficial or not well organized. Good summary however on P35-L20-24. It would be helpful to include a paragraph on the ISA that summarizes the complexity of nutritional interactions as these interactions may be physiological (deficiency programs homeostatic regulators to absorb and retain needed elements), biochemical (competition between Pb and other elements for transport and binding sites), macronutrients may alter Pb bioassessibility, genetic variants may modify all of the above.

P4-38,L36-37. "Factors that may affect in vitro predictions of RBA of interior dust Pb could include…" Suggest clarify sentence for potential ambiguity. The 'prediction' is for in vivo RBA. In vitro RBA is measured. Secondly, while the in vitro measurements will be affected by factors such as particle size and composition, etc. the 'predictions' should hold as the in vitro → in vivo predictions are particle dependent.

P4-46, L19-21. "Approximately 7-39% of the maternal Pb burden transferred to the fetus was derived from the maternal skeleton…" The relative contribution of maternal skeletal lead stores and contemporaneous environmental lead exposures to the fetal skeleton is not easily generalized as the maternal skeletal burden on the environmental exposure may vary significantly – independent of each other. Moreover, I believe the skeletal lead levels of these cynomologus monkeys were quite high diminishing the human relevance of these studies.

P4-39,L23 vs. L4-49,L12. Contradiction → Page 39 reports that 1% of body burden is in blood; Page 49 reports 5%.

P4-49,L15 vs. P4-54, L7. Contradiction → variously report either hemoglobin or ALAD as the major lead binding protein in blood.

P4-53,L22-30. Most proteomic and metabolomics data are highly left censored and statistical strategies have been developed to deal with this issue, with and without imputation. It may be appropriate to revisit this issue using newer methods.

P4-61,L9-18. Although Mitchell et al, and Hernberg et al. discussed blood Pb, and blood ALAD activity in the context of lead exposure I suggest the their use as a "biomarker of lead exposure" (L11) is vague and potentially mislead in the context of the ISA. This limitation is due to the effects of ALAD alleles on Pb binding and ALAD activity that confound relationship to lead exposure.

P4-65, Figure 4-9, 4-11. Remove "upper", "middle" , lower" labels . Suggest remove panel with time-averaged blood Pb

Comments related to fluoride and lead:

The ISA briefly and superficially discusses the potential role and impact of fluoride on drinking water lead following leaching from plumbing (p2-78; p4-21) or experimental skeletal lead accumulation in the rat (p6-3). These brief citations suggest that fluoride may increase leaching and by implication lead levels in drinking water. In contrast to the ISA's brief conclusion, Triantafyllidoua and Edwards do not mention fluoride in their recent extensive review (Lead (Pb) in Tap Water and in Blood: Implications for Lead Exposure in the United States. Critical Reviews in Environmental Science and Technology, Volume 42(13), 2012 DOI:10.1080/10643389.2011.556556).

Consistent with the ISA, Coplan et al. review numerous studies purporting to show the importance of fluoride and blood lead levels. (*Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals*. NeuroToxicology 28 (2007) 1032–1042). However, this paper also includes sections titled, "4. EPA's refutation of SiF adverse health effects" and "5. CDC's dismissal of an SiF/PbB linkage". Thus, the potential health interactions of Fl and Pb may be charged with scientific and/or policy conflicts. Therefore, the ISA should be revised to provide a careful, more nuanced review of this issue.

Comments related to clarification:

P4-21-L20. Define the model used my Miranda et al.

P4-30. Section 4.2. Consider moving (burying) the "dermal absorption" text at the end of 4.2.1 rather than leading with the section with this less important route.

P4-32-L10-13. I believe that "bioavailable' should be "bioaccessible"

P4-34, L14. Sentence "Eating breakfast…" is not clear. Is breakfast proportional to blood lead? Inversely proportional? Is lead found in breakfast foods or is breakfast a bioavailability/bioassessibility issue?

P4-36, L13. Relative bioavailability (RBA) is defined as fraction (L13) but presented as percentage.

P4-40, L28. 'toxicologically' → kinetically

P4-41, L3 clarify to 'limited capacity of Pb-binding proteins in RBCs…"

P4-44, L13 – clarify to "nonexchangeable" (except by bone resorption/bone remodeling) pool of Pb in bone…"

P4-45, L13. "A key factor affecting Pb uptake into bone the fraction of bone surface in trabecular and cortical bone adjacent to active bone marrow." This paragraph does not convinceably describe why this fraction is a "key factor".

P4-47, L32. "Estimates of urinary filtration of Pb from serum" → Estimates of urinary filtration of plasma

P4-62,L28. "…measure of Pb dose." → "…measure of long-term lead exposure.

P4-67,L25. "…the effects of bone Pb…" → "the correlation of bone Pb…"

P4-99, Figure 4-20. Note is confusing. What is the solid line?

Dr. Michael Rabinowitz

General Remarks in Response to Charge Question:

This draft is much improved, particularly with the inclusion of these summary chapters and by the placing of the causation discussion in the Preamble. This allows a reader to get a clear picture with sufficient, but not excessive, detail. I must assume some readers will only read Chapter 1, and a few more might read Chapter 2. In that role it appears to be an effective and useful resource. Looking at Chapter Five and how its content was captured by Chapter, it appears adequate.

Additional Specific Comments:

In that my pre-meeting comments contained many small corrections and suggestions to wording with page and line citations, here I present only the more general and salient comments.

A: Some history could be added : It was recognized early that unlike other priority pollutants, such as ozone, lead exposure is multi-media, and that regulating air exposure did reduce total exposure, but other sources and pathways were at work.

Also, for background we should remind readers that most of us get most of our daily lead intake from dietary sources.

Additionally, soil naturally contains some lead. soil and biota have evolved to accommodate this fact. For example, many plants (grasses) sequester large amounts.

Lead is not biomagnified nor bio-accumulated (to use a more accepted term). This is in contrast with mercury, where fish achieve higher concentrations than algae, and carnivorous fish have more than algae eaters.

B: Maybe, also add something about the uncertainty about the permanence or reversibility of lead effects. Some effects are reversible, such as interruption of the heme pathway, while others such as nerve conduction appear permanent.

C: Please, change the word "measurable" referring to lead levels. It is not helpful, and is only a tribute to analytical chemists. "Elevated " concentrations would be suitable.

D: Looking at the slopes which summarize the air lead-blood lead relationship, Table 2-7 for example and elsewhere, it was tempting for me to see how me own earlier experimental assessments of this slope compare, both from clinical work in Los Angeles and epidemiological work in Boston. I mention the Los Angeles experience because it is unique in measuring lead intake directly, not as a correlation, but as a matter of laboratory medicine. Following the template of the table these two estimates follow:

Adult Populations
Ref hero id 815254 Magnitude of lead intake from respiration
Location: West Los Angeles
Years: 1973-1975
Subjects: Adult Male Veterans (n=5)
Analysis: Long term metabolic balance ward with constant duplicate diets, stable isotope dietary tracer with and without HEPA filtered air.

Model: linear changes in blood lead from changes in air, incomplete labeling of blood from dietary lead, and urinary output exceeding dietary uptake
Blood Pb: mean 19, range 17 to 25 ug/dL
Air Lead: 0.07 to 1.9 ug/m^3
Slope: 4.4

Children Populations
Ref hero id 093549 Lead in umbilical blood, indoor air, tap water and gasoline in Boston

Location: Boston
Years: 1980-1981
Subjects: Umbilical cord consecutive births n~7000
Analysis: Regression of 14 monthly mean cord blood (n~ 500) against mean indoor air lead (n~12)
Model: Linear
Blood Pb: 4.3-7.0 ug/dL (monthly mean)
Air Lead .02 to .2 ug/m^3 (monthly mean)

Slope: 9.1 (est 7 to 10) $r=0.71$ $p<.01$

Although there was a statistical relationship between monthly average air lead and monthly average cord blood, many other factors were much more predictive of blood lead levels, including parity, smoking, and indoor dust lead levels. Regarding subsequent childhood blood lead levels in this population, they did not correlate with their indoor air lead levels. Soil lead, dust lead, lead paint and refinishing activity were strong predictors.

We all recognize this blood lead slope is not a constant of nature, like the charge on an electron, where successively better measurements will yield better estimates of a specific underlying value. Rather the slope has a spread in values, reflecting variations seen among populations.

These two additional values, 4.4 and 9.1, with different populations at different air lead levels, add to the picture. Taken with the other studies, there is real consistency, within a factor of two, but also variations among populations and are evident. One would expect the slope would be steeper for children compared to adults because of their higher metabolic rate.

The broader issue, which is not fully discussed, is how this slope uncertainty translates into uncertainty in setting an air standard.

E: Regarding confounder so lead's effects on child development, I had suggested displaying nested models to help show the extent to which Pb is an independent risk factor in the epidemiological modeling, where so much variance is shared. We should be able to see the extent or strength of confounding in the various studies, and see the effect size for Pb along with the whole model's predictive power (r-sqr). That Pb can be shown to have a non-zero coefficient in multiple regression models, for example, of children's mental performance, is insufficient. Because of the extent of the confounding, this is different than showing that Pb is an independent risk factor. Pb and these other risk factors share considerable variances, particularly in some of the higher risk populations, where Pb exposure and other risk factors often coexist.

The relative size of this non-zero coefficient, the size of the Pb effect, should be shown in terms of the model r-sqr, or goodness of fit. How good is that model's fit with and without a Pb term in a series of nested models? Does the r-sqr increase significantly (Wilks criteria) when a Pb term is offered? How much do the confounders' strength shift towards the Pb term, with which it shares variance, when Pb term is introduced? This would help a reader see how much is caused by Pb compared to other risk factors, preventable and otherwise.

My concern is that at progressively lower Pb levels, where Pb effects are small, blood Pb can still be measured relative accurately (often to 2 significant figures) but other, stronger variables, such as maternal education or richness of the child's home environment can be more difficult to measure, subject to reporting errors, and are often entered as broadly categorical variables, while lead is a continuous variable. At these lower but measurable, Pb levels, Pb effects get lower, but the confounders relative strength increases. For these reasons, at these low levels, effects attributed to Pb by statistically adjusting for the other covariates, may overstate the case. For that reason showing models with and without the Pb term would be useful. Also, it may help identify the more critical studies in terms of seeing a "clean" Pb effect.

Now, let me suggest in tabulating the studies, show both the raw lead coefficient and the adjusted value. The strength of the confounding in that study would be indicated by the difference between the raw and adjusted vales. This would guide the reader in weighing the various studies so as to put less weight on studies with extensive confounding.

F: The role of fluoride in drinking water in elevating blood lead levels needs more elucidation. The effect may be from increasing the plumbo-solvency of the water, its ability to dissolve lead from metals, as well as fluoride effect of skeletal metabolism of trace divalent metals. The form of the fluoride additive and the relevant dosages are unclear.

G: About causation and our ability to make comments about degrees of certainty, I suggested turning to the legal profession for some guidance or examples. In civil cases of money damages the level of proof

is "more likely than not" , while in criminal cases "beyond a reasonable doubt" is the test. As EPA evolves its considerations of causality something might be gained from the legal precedents.

H: Now that we are able to be concerned with progressively lower lead levels, it might well be time to revisit the leach-ability of lead from glasses, ceramics, and tableware. Years ago when we getting more than a hundred ug/day in our diet, the few ug from lead glazes were insignificant, but now with just a few ug/day ingested from all sources, this might be a more weighty sources of exposure.

Dr. William Stubblefield

General Comments

In preparing these comments I have reviewed the document, *Integrated Science Assessment for Lead (2nd External Review Draft*), with specific attention given to Chapter 7: Ecological Effects of Lead.

Charge Questions Addressed:

Preface, Preamble, Chapters 1 (Executive Summary) and 2 (Integrative Summary)

The CASAC panel offered a number of recommendations to enhance the organization and presentation of the evidence in the ISA. An Executive Summary has been prepared and is included as Chapter 1. As part of the development of the Executive Summary and restructuring of the integrative overview chapter, Chapter 1 materials have been revised and moved, specifically: (a) the more general sections on the development of the ISA and the causality framework are being placed in a Preamble that can support all ISAs; (b) the introductory sections specific to this ISA describing the ISA development and scope are placed at the beginning of Chapter 2; and (c) sections on legislative background and history of previous reviews are contained in a Preface in the front matter of the ISA. The intent was to bring the integrative overview discu·ssion to the front of the document, thus making it more accessible to the reader, and to streamline the ISA organization.

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy or presentation of these summary sections and the conclusions therein.

In addition, please comment the extent to which the discussion of the health effects evidence in Chapters 1 and 2 reflects the revisions to Chapter 5, which were designed to characterize the weight of the evidence for specific endpoints as well as the strengths and limitations of the studies.

Chapter 7 - Ecological Effects of Lead

The causal statements for ecological effects discussed in Chapter 7 have been reevaluated as advised by CASAC. There are now separate causal determinations for terrestrial and aquatic biota for each endpoint under consideration. In addition, the chapter now incorporates additional findings from the 2006 Pb AQCD on the effects of Pb on ecosystem receptors, an enhanced discussion of bioavailability

and bioaccessibility, and separate discussions of marine and freshwater toxicity in the aquatic ecosystem section.

Please comment on the adequacy of these various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information.

The following are my preliminary responses to the charge questions. I have focused most of my attention on the Chapter 7 concerns, but many of the comments are equally applicable to Chapters 1 and 2. I have also focused primarily on what I consider major concerns; greater detailed and editorial comments will be provided at the meeting.

1. *EPA staff and technical support contractors are to be congratulated for the improvements in the overall document as a result of the revisions.* The document is more readable and comprehendible and the organizational revisions have improved the overall flow and technical discussions in each of the chapters and subsections. Increased literature search efforts have identified a number of studies that greatly improve the database and understanding of potential effects on ecological receptors attributable to lead. It is noted, however, that in some cases, industry data developed for the purposes of European REACH regulation requirements have not been considered in the document. As previously pointed out by this review panel, additional data are available that may or may not improve the overall understanding of lead effects on ecological receptors. At a minimum the report should acknowledge the existence of these data and state justification for not considering these data in the preparation of the AQCD.

2. *Causal relations*: A great deal of effort and focus in this document go toward the review and evaluation of whether lead exposure can result in a variety of effects to exposed terrestrial and aquatic organisms. In each case, literature data are identified and a conclusion rendered as to whether the observed effect can be causally linked to lead exposure. The results of these analyses are contained in Table 7–2: *Summary of lead causal determinations for plants, invertebrates, invertebrates*. These conclusions may be misleading, leaving the reader with the impression that air quality exceedances are leading to adverse effects in exposed terrestrial and aquatic systems. When in fact, what is actually presented is an array of potential adverse effects, enzymatic responses, neurological or behavioral responses that an organism may or may not exhibit depending on the concentration of lead that they are exposed to. Little information about the exposure concentrations at which these endpoints are affected and no discussion about the relationship between atmospheric lead concentrations and observed adverse environmental effects is provided. In some cases, for example Section 7.4.2.6: *Survival-aquatic biota,* a risk assessment-based approach appears to have been applied to the evaluation of potential effects. In this section it is noted that "Freshwater biota that exhibit sensitivity to Pb in the range of Pb concentrations measured in US waters […] include some species of gastropods, amphipods, cladocerans, and rotifers although the

toxicity of Pb is highly dependent upon water quality variables as DOC, hardness and pH." This suggests a comparison of reported toxicity values to measure environmental lead concentrations and a conclusion that environmental lead concentrations may be sufficient to cause adverse effects and exposed organisms. No discussion is offered as to whether these environmental concentrations result from atmospheric deposition, point or nonpoint aquatic discharges, or natural background concentrations. In most of the other endpoint discussions, no reference whatsoever is provided to the concentrations at which adverse effects are observed and "real world" environmental exposure concentrations, thus leading the reader to conclude that adverse effects are resulting from current exposure conditions [and by inference to lead atmospheric discharge concentrations].

3. *Nontraditional endpoints*: Traditionally the US EPA has limited the use of potential endpoints to those "higher order biological responses" (e.g., survival, growth, reproduction) that can be directly related to "population level" effects. Alternative endpoints such as physiological stress, hematological effects, biochemical and enzymatic responses, and neurological and neurobehavioral alterations may be affected by lead exposure but the interpretation of these observed responses and their meaning on a population level remains in question. This document identifies these endpoints as important observations and attributes these endpoints to lead exposure. This approach is appropriate if EPA has changed their stated policy regarding the importance and use of these types of endpoints. And suggests that in the future EPA should/will be considering these endpoints in the methods employed for developing contaminant criteria/standards.

4. *Prediction of environmental lead concentrations attributable to atmospheric deposition.* Although not specifically part of Chapter 7, this point is key to the interpretation of the entire AQCD. Measured environmental lead concentrations are a result of a number of potential inputs, e.g., atmospheric deposition [e.g., stack emissions and blown dust from contaminated areas], point or nonpoint aquatic discharges, or natural background concentrations. Little use can be made of environmental monitoring data if we do not have a firm understanding of the sources that may have resulted in the measured concentrations. It is therefore critical that EPA take steps to understand the role of atmospheric lead deposition and, if appropriate, to develop atmospheric deposition models that will allow the prediction of terrestrial and aquatic lead concentrations and attribute those concentrations to atmospheric sources.

Dr. Ian von Lindern

Preface, Preamble, Chapters 1 and 2

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy or presentation of these summary sections and the conclusions therein.

Addition of the Preamble and Executive Summary has markedly improved the readability and comprehensiveness of the document. The previous draft was well-edited, as are the added sections. The explanation and summaries progress from the most brief to a relatively full (but nevertheless) concise presentation of the salient issues brought out in the ISA. The historic perspective incorporating the findings of the previous AQCD findings are a particularly strong addition to the document.

In my opinion this is an excellent document that is both comprehensive and well presented as were the AQCDs produced in 1977, 1986 and 2006. However, I believe there are three fundamental weaknesses that detract from the tradition of EPA providing the seminal, scientifically sound review of the existing knowledge of lead poisoning that was fundamental to developing and implementing effective lead health policy and response throughout the world.

1. The scope of the review has been amended to an insular and less comprehensive document that will have adverse effects on the ability of both the EPA and other parties, who have historically relied on these reviews, to effect comprehensive and holistic policy.
2. The failure to collect and or assess information relative to the use and disposition of lead in US commerce, and the decision to exclude globally representative exposures, precludes the Agency from considering the effects of policy decisions in media other than air and beyond the boundaries of the US.
3. These factors, combined with diminished monitoring over the past two decades and reliance on outdated emissions inventories, reduce the Agency's ability to assess risk across the nation. As a result, EPA must rely on theoretical models, as opposed to observed exposures, to conduct appropriate risk assessments. Because so little additional information has been collected in the areas of use, consumption, emission factors, and ambient monitoring, these models will be a repeat of those supporting the 2006 documents, and will be decades out of date.

General Comments

The fundamental premise underlying the relative weakness of the ISA, in contrast to earlier AQCDs, can be found on page xlvi of the Preamble that states "*… the intent of the ISA is to provide a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the NAAQS, not extensive summaries of all health, ecological and welfare effects studies for a pollutant."*

EPA, subsequently, limits the ISA and the definition of *"policy relevant science"* to the *"peer reviewed literature"* and to "*exposures within one to two orders of magnitude of those currently observed in the US".*

These limits, nevertheless, have resulted in a massive document that does a masterful job of recounting the findings of the 2006 AQCD and the state of knowledge with respect to the peer-reviewed literature from 2006-2010 regarding the health and ecological effects of low-level lead exposure in the US, Europe and Australia. An entire volume of 550 pages is dedicated to Chapter 5 the *Integrated Health Effects of Lead Exposure.* The length and detail presented in Chapter 5 is justifiable, in a health-centric sense, as a considerable amount of new information has accumulated in that relatively short amount of time.

In contrast, however, only 18 pages are reserved for *Sources of Lead* of which relatively little of the information is new. Moreover, virtually nothing is found in over 1100 pages of lead-related information regarding the uses or rates of consumption of lead, the role of lead in US and international commerce, lead production, the level of imports/exports of products and wastes, or the ultimate disposition, recovery, recycling or disposal of lead-containing materials.

The same deficiency was noted in the last NAAQS review and the 2006 AQCD was admittedly bereft of this information in comparison to the predecessor documents. It was clear at that time, as in previous iterations of the AQCD, such information was not to be found in the peer-reviewed literature. In the 1977 and 1986 AQCDs, source, production, and fate information was provided by an active lead industry in the US, and by EPA staff development and synthesis of trade, professional and commerce data sources, or so-called *grey literature*. Among CASAC's responsibilities in those years was to review the scientific credibility of those analyses and trade data, and its use in the criteria document, and ultimate formulation of lead policy.

The EPA has, through its change in approach, conveniently both made its job less challenging and short-changed the policy-makers (also making their job easier) by adopting a rule, exemplified in the ISA and, pre-destined to similarly limit policy in a myopic and insular way that concludes: *If it's not in US air, we don't care.*

The analyses then point out that air lead decreased by more than 90% from the 1970s to 2008. Similarly, dramatic decreases in blood lead levels in the US population and other biota and environmental media

have also been observed. This is good news for the children, general population, and flora and fauna of the US; and should be considered a remarkable success in environmental health regulation.

However, a couple of points remain that, perhaps, question the validity of an approach that ignores the numerous areas of this planet that live two orders of magnitude above current US exposures.

i) In the last analyses of US commercial use of lead in the 2006 AQCD, domestic lead consumption had increased to levels near the peak tetra-ethyl lead years, presumably for batteries and the consumer electronics industry. However, domestic lead production had diminished as drastically as ambient air levels. At the primary smelting level, production will soon be zero as the last US smelter closes, and responsible recycling capacity in the US is limited.

   The absence of data or analyses in the ISA suggests that EPA, apparently, has little knowledge of where all this lead comes from, how it is used, how much is recovered or recycled, or its ultimate disposition. This is even though demand may likely increase as electric cars hit the markets. Rather than find out, the agency has, through the ISA, devised a way to avoid either finding out or admitting this deficiency.

ii) Beyond the US borders, in what can only be considered tragic, on a global basis today - more children are lead-poisoned, at higher absorption levels, unprecedented mortality rates, or with severe brain trauma doomed to lifetimes of stupidity and dependency - than has ever been recorded in the peer-review literature.

For EPA to apply the -*"If it's not in US air, we don't care"* position to these children, the Agency is seemingly convinced that US lead consumption and poisoned children in other countries are unrelated. However, it seems naïve to believe that a standard, with the policy implications of the NAAQS, has not influenced the magnitude and associated costs of production, recycling, recovery and disposal of lead and lead waste, and metals prices. There are numerous examples of poisoned children living in the vicinity of smelters producing lead for the US market; of discarded US car batteries poisoning children in Mexico, Latin America and the Caribbean; and of families poisoned from recovering metals from US e-waste in Africa and Asia. Previous iterations of the AQCDs provided a sound scientific basis for policy considerations in the US and were relied upon by other national and international entities to assess, bring attention to, and effect health responses to these situations. EPA, in the past, has and should continue to, take great pride in this laudable role. The ISA is silent on these issues.

Moreover, the substantial increases in both commodity and precious metals prices over the last five years have lead to unprecedented increases in both formal and informal mining, smelting and waste recovery across the globe. Yet the only mention of *global lead* in the ISA is in reference to "… only fine particulate lead is of consequence on a global basis, as most large particles fall out near the sources." This definition implies that only those particle emissions capable of dispersing into this country from overseas are significant. It is quite possible that the US sends far more lead waste across the oceans in container ships than the upper atmosphere delivers in small particles to the US.

It seems appropriate for the EPA through the ISA process to inform the Agency decision-makers, the CASAC, and eventual policy-makers and reviewers regarding the disposition of lead in US commerce, the health and environmental effects playing out on the global stage, and any connections or interactions that may be at play. It also seems incumbent on the Agency to develop the available information and subject it to the same scrutiny and evaluation that has been so well done regarding low-level health effects within the current insular viewpoint.

Two examples of current events in the outside world that could be of interest and value to a less myopic ISA, and in providing a vetted information base for responsible policy development are discussed briefly below, There are many more.

1. The USEPA has recently concluded Trustee Settlements with Responsible Parties to guarantee cleanup of lead contaminated sites throughout the United States under CERCLA. These settlements run to billions of dollars with multi-national corporations. These funds depend on profits made by these companies producing metals largely in underdeveloped countries that do not subscribe to US pollution control standards. In these cases, the US standards and policies have contributed to the export of the US national production capacity to foreign countries subject to health and environmental exploitation. The concurrent need for these corporations to route profits to fund US cleanups could be coming at the expense of pollution control, thus exacerbating the damage done to children in these communities. Moreover, as the ISA demonstrates, human health risks in the US have been substantially diminished. As a result, the vast majority of the cleanup activities being undertaken in this country, with these trust monies, addresses ecological and water quality remedies. However, these laudable improvements in US "ecological and welfare effects" may well be coming at the cost of childhood lead poisoning in populations most vulnerable to those SES and concurrent disease risk co-factors so well identified in the ISA.

2.) There are today sites in Africa where children are dying of lead encephalopathy, in at least one case, at staggering rates. Some villages in northern Nigeria lost more than 25% of children under five years of age. An estimated 400-500 children died of lead poisoning in less than one-year in an overall population of 10,000. More than 2000 children, with blood lead levels averaging greater than 130 ug/dl, at presentation to clinics, have received multiple rounds of chelation treatment.

Another 20,000 people are likely lead poisoned and receiving no treatment. Among those are 1500 children under age 5 living in mud-hut homes with soil lead concentrations more than 1 % lead, with blood lead levels greater than 70 ug/dl, who cannot be provided treatment. A cohort of more than 5000 women, expected to have 5-10 children in their reproductive life, have persisting blood lead levels greater than 70 ug/dl. These populations live on less than $2 USD/day. More than 90% of the children presented for chelation have malaria. Mumps, measles, polio and meningitis are endemic in these communities. Last year more than 250 children under age 5, in hospital, were being simultaneously treated for lead poisoning, malaria, malnutrition and cholera,

It seems inappropriate that these situations are not considered "policy relevant" and are excluded from consideration in an "Integrated Science Assessment for Lead". It seems that, at least, a

scientific review of these situations be conducted to assess whether consideration of these unprecedented case histories can contribute to the knowledge base regarding childhood lead poisoning, Moreover, it would seem appropriate to provide a properly vetted information basis for US policy-makers to assess whether regulation of lead in the US facilitates, contributes to, or possibly could help alleviate these tragedies.

Specific Comments:

Preamble Page lxvii, line 3: The History section for the NAAQS should also include (with similar reference to the key decisions) the pre-promulgation history, particularly noting that the EPA initially proposed regulating airborne lead through Best Available Technology (BAT) controls on point-source emission sources in 1974-75. The EPA was subsequently sued by public interest groups and eventually forced by the Courts to develop the NAAQS. Similarly, the promulgation was opposed and delayed by suits brought by lead industry advocates. These lawsuits were not resolved until 1980 when the NAAQS became effective. This history is important to underscore the point (well documented in the ISA discussion that follows in the document) that outside intervention by litigation has routinely been required to assist and provide guidance to the EPA in undertaking responsible review, assessment, and promulgation of lead regulation.

Preamble Page lxviii, line 29: A brief description of the actual computational basis specifically justifying the .15 ug/m^3 standard, and the rationale for averaging times would be helpful.

Executive Summary Page 1-2: The Section 1.2 discussion refers to Figure to Figure 1.1. The Figure is excellent and well described later in Chapter 4, but the discussion here seems overly brief and does not convey to the uninitiated reader the complexity of the Figure, nor the pathways the Figure represents. There seems to be a need for some transition language for the text immediately preceding and that following Figure 1.1, which moves from environmental pathway discussion abruptly to blood lead.

Chapter 2 Page 2.5 line 19: Several times in the discussion the term 0 is used to refer to the Preamble. This seems distractive and could be confusing to uninitiated readers.

Section 2.2.1 Page 2-6 line 9 and Page 2-10 line 6: These discussions refer to "… on a global scale lead is primarily associated with fine PM." In this context, and in similar discussions throughout the document, it seems that EPA by implication considers only those lead emissions that reach the US are significant on a global basis. In turn, this seems to imply that EPA defines the global atmosphere as a "source" rather than a transport mechanism, or exposure medium; that foreign populations are emitters rather than co-receptors; and that "local" emissions beyond US borders are unrelated to US policy.

Table 2-1: Including earlier concentrations observed in the US over the past few decades and those observed globally today would serve to put these relatively low exposures in an historic and international context.

Page 2-11 line 31: Description of the term "personal cloud effect" would be helpful.

Table 2-7: This Table does not include the slope estimates, nor the supporting studies, used in promulgation of the NAAQS in 1977-78. As this was the basis for EPA's NAAQS for over 25 years, it seems it should be listed for contrast with those studies reviewed to support the more recent standard and accumulating evidence.

Chapter 3 - Source to Concentration

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. Is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

Sections 3.2 and 3.3: The EPA seemingly knows little about the use, consumption and ultimate disposition of lead in the US (see earlier general comments). These sections generally report the same deficient information developed for the 2006 AQCD. The synthesis of this lack of information should note the scarcity and the implications of being uninformed in this capacity.

Sections 3.4 and 3.5: This Section does a good job of describing the methods and network systems and the results of the various monitoring efforts. However, it is difficult to get any real answers to important questions in these sections. This in contrast to the health effects and ecological sections where the document provides synthesis analyses and draws significant conclusions with regard to causality, mode of action, potential effects, etc. It is difficult in the air monitoring sections to determine:

Which sites are monitored for compliance or exposure characterization?
How representative are these sites of the remainder of the country?
How many observations exceed health significant exposures or criteria?
What are the sources of those high levels?
Are measures being undertaken to control those sources?

The most informative presentations are in Tables 3-7 through 3-9 and Figures 3-23 through 3-26. These tables and figures seem to suggest that non-source- oriented lead TSP, lead-PM10, lead-PM2.5 show no lead problem with whatever is being monitored. Does this mean no lead problem for these sites, for similar sites in the US, or that these techniques are inappropriate?

Source oriented TSP, however, seems to a cause for consternation, at least at those sites being monitored. The mean concentration for all sites seems to be consistently well above the health significant level, at least for these sites. What does this imply for the overall US? What confidence does the EPA have that all significant sources are being monitored? This is particularly troublesome when it seems the Agency has little idea where, how, or in what quantities lead is used, consumed, or disposed.

In summary, there continues to be no "take away" message with regard to these data and analyses. What is the appropriate monitoring technique? One method shows 2/3rds of all source oriented sites are out of

compliance across the U.S.; the other method shows 3 of 323 sites exceed the criteria, but does not specify source type. Does the latter method appropriately reflect the risk associated with these sources?

If 2/3rds of source oriented sites are out of compliance, how many of these sites are there in the country? Are there only 22 that are being effectively monitored, or hundreds or thousands not being monitored? What populations are exposed by these sites? How do these sites relate to the National Emissions Inventory presented earlier in the Chapter, or are these the other anthropogenic sites, for which there is no inventory? It seems there should either be answers provided to these questions to support a national risk assessment, or an indication that the problem is not appropriately characterized by current source inventory and monitoring efforts.

Page 3-13 line 2: spelling of "simualated"

Page 3-53 line 23: spelling of "were" where?

Section 3.6.8 and other locations: References to tissue lead concentrations should always indicate whether these values are wet weight or dry weight basis.

Chapter 4 - Exposure, Toxicokinetics and Biomarkers

The exposure section of Chapter 4 includes additional discussion of the relationship between airborne Ph-particle size distribution and exposure by inhalation and ingestion (e.g., hand-to mouth). Cross-referencing to Chapter 3 further emphasizes measurement errors and uncertainties that may affect exposure assessment for air Pb. A new section on exposure assessment methodologies was added that includes discussion of exposure representation within the IEUBK model and exposure modeling techniques.

The revised toxicokinetics section of Chapter 4 expands discussion on the effects of both past and current Pb exposure on blood Pb levels. Studies that followed blood Pb levels in individuals following cessation of high Pb exposure occupations and in children over the first several years of life were added. The section on bone Pb measurement was expanded. Air to blood slopes were reevaluated across the range of air Pb concentrations available in a given study with an emphasis on the central tendency of air Pb concentrations in each study.

With consideration of these revisions, please comment on the accuracy of the interpretation of the science. Are uncertainties and limitations of relevant data, methodologies and approaches adequately discussed? Where appropriate, please provide specific recommendations to refine the scientific interpretation and/or improve the representation of the science.

Chapter 4 is well organized, comprehensive and provides an understandable, accurate and balanced interpretation of the science as related to exposure, toxicokinetics, and biomarkers. The material added to this draft not only improves the readability of the material, but puts the information in the context of how it might be used to assess exposure and alternative techniques. The cross reference to Chapter 3 is

an important addition, as uncertainties and insufficiencies in the database are key to reflect in any attempt to assess exposures.

The addition of the historical perspective provides important insight as to how the concentrations and relative intakes have decreased in association with the phase down, industrial source curtailment, and decrease in lead content of consumer goods over the past three decades. Both Chapters 3 and 4, however, remain somewhat biased toward the gasoline phase down in this regard and would be better served by noting that significant emission and air lead reductions achieved in the vicinity of point sources. The major reductions in point source emissions were achieved through a combination of pollution control and elimination / curtailment of the industry. Two important aspects of this realignment go unmentioned. These sources were also significant with respect to other metals and pollutant exposures that were similarly reduced. The export of the mineral processing operations also had profound effects with respect to risk co-factors in the US and exposures and systemic effects both here and abroad. Particularly important in the US were effects associated with numerous other metal-related pollutant concentration decreases in other media and levels of ecological risk, both locally and regionally. These effects were both attendant to and independent of the phase down and curtailments in industrial emissions.

The addition of the IEUBK oriented discussion illustrates the interdependence of various exposure routes. This is followed by an excellent discussion of other media that effectively summarizes the current state of knowledge with respect to relative significance of these media in acting as sources, in pathways, and as receptors. It is noted that exposure sources and pathways are moderated by behavior, housing, lifestyle and cultural patterns. These patterns vary immensely for developing and middle-income countries and cultures, as compared to the US, Europe and Australia, where nearly all the science has been developed. It might be noted, as a prelude to Section 6, that many foreign and immigrant populations in the US engage in ethnic and cultural behaviors leaving them more susceptible to lead intake and uptake.

Chapter 4 provides a concise and well-developed discussion of the toxicokinetics that is reflective of the current understanding and practice in risk assessment activities. The overall discussion of the health significance and interrelationship of the toxicokinetics and biomarkers is informative and well presented. This chapter also provides a concise summary of exposure / blood lead relationship representative of the current scientific consensus for this important segment of risk assessment process.

Chapter 5 - Integrated Health Effects of Lead Exposure

In Chapter 5, the integration/synthesis of evidence between epidemiologic and toxicological studies and across related outcomes has been expanded throughout the text and in summaries of individual endpoints. In the summary and causal determination sections, we have described more explicitly the weight of evidence for each endpoint within a broad outcome category and specified the particular endpoints that contribute most heavily to the determination of causality. We have noted, where applicable, uncertainties regarding the specific Pb exposure periods, levels, frequency and duration that

contributed to epidemiologic observations and included additional details and discussion of study limitations.

Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.

Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiologic studies, in particular: the increased emphasis on toxicological findings most relevant to Ph-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Ph-associated health effects. Has the coherence of findings among related endpoints been sufficiently described? Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.

Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). Are inferences regarding the specific Pb exposure scenarios (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?

Chapter 5 is monumental and is an excellent and impressive summary and synthesis of a subject area in which incredible advancements have been accomplished both in the last three decades and last five years.

Chapter 6 - Potentially At-Risk Populations

The introduction to Chapter 6 has been revised with expanded discussion to better capture the intricacies associated with characterizing populations potentially at greater risk for Ph-related health effects. Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

In addition, please comment on whether the designation of some factors as having limited evidence adequately reflects the knowledge base considered and strength of evidence available.

Chapter 6 does an outstanding job of synthesizing the information from the previous chapters and identifying those populations potentially at risk due to lead exposure. However, it might be noted that these are hypothetical populations, as an effective national risk assessment is not possible due to the lack of appropriate exposure data.

Chapter 7 - Ecological Effects of Lead

The causal statements for ecological effects discussed in Chapter 7 have been reevaluated as advised by CASAC. There are now separate causal determinations for terrestrial and aquatic biota for each endpoint under consideration. In addition, the chapter now incorporates additional findings from the 2006 Pb AQCD on the effects of Pb on ecosystem receptors, an enhanced discussion of bioavailability and bioaccessibility, and separate discussions of marine and freshwater toxicity in the aquatic ecosystem section.

Please comment on the adequacy of these various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information.

Chapter 7 in and of itself is a major contribution to literature and understanding of this long-neglected aspect of both the mechanisms and the adverse effects of lead on US ecosystems and public welfare.

Dr. Gail Wasserman

Chapter 1:

1-15 Discussion of Public Health Significance. I found this to be informative and well done.

Chapter 2:

Substantive concerns:

2-55 Discussion at top of page. This figure still troubles me. To be most accurate , the ISA needs to explicitly indicate that it is a *model*, for *illustrative* purposes. It's really not data-based; especially at the low end, where the model would apply only if exposure/outcome relationship is the same, or of similar magnitude, across all points on the exposure curve. This place where we lack data to confirm or disconfirm the model needs to be explicitly stated.

2-66 and 2-67 This discussion, that refers to the non-linearity of the exposure/outcome association I think has implications for that figure on page 2-55

Smaller edits:

2-15, L 12 I think there is a word added or missing in the parentheses "(prior symptoms of ADHD)"

2-48, Table 2-4 Another place remains where "neurological" remains, and should be ? neurodevelopmental????

2-54 L 15 Another place remains where "neurological" remains, and should be ? neurodevelopmental????

2-56 L 13 "It is shown……" needs a citation

2-72 Table 2-8 I think that the entry should refer to "Exposure to cigarette smoke" rather than to "Smoking"

2-80 Table 2-10 Under Neurobehavioral Effects, there is a word missing. Should read "and also misconduct **and** delinquent behavior"

Chapter 4:

4-82 Figure 4-16. Title should read "……among US children (1-5 years old **at baseline**)" otherwise it is confusing.

Chapter 5:

Charge questions:

1. Does the revised discussion of evidence and causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths/weaknesses of studies that comprise the evidence base.

Overall I think this version reads better, and is far more grounded. This version is more thorough regarding where we lack definitive answers to questions about exposure characteristics and the weight of the evidence.

5-62 to 5-64 In the presentation of the papers from Asia of the exposure/IQ association, when expectable associations between social factors and intelligence do not appear to be significant, it is not clear WHAT this means. Either this reflects likely cultural differences in which features of the social environment do and do not contribute to intellectual functioning, or it means that one or another of the constructs (either the measurement of intelligence or measurement of the social environment) is badly defined. To me, this is a red flag that study results should be given less critical weight. Perhaps the nature of this limitation could be better spelled out, as it is likely these studies are not capturing the constructs that should be adjusted for in those settings.

Section beginning on 5-19. The discussion of ADHD needs to distinguish between (1) measurement that relies on the cardinal symptoms of the disorder (ie inattention, impulsivity, symptoms are usually indexed by parent- or teacher-report on a scale, such as Conners or CBCL) and (2) that which is based on presence of the clinical disorder itself. I suggest that the authors specifically consult the DSM for information supporting the distinction between symptoms and disorder. This is a conversation we already had about measuring delinquency via items on a subscale that is labeled “delinquency” but that may include a range of behaviors (as in the CBCL subscale of that name) , and juvenile delinquency (which is a legal term, referring to being identified, usually by juvenile justice authorities, as breaking a law). Discussion of the underlying constructs in attention problems would allow for easier mapping onto animal work. In the discussion of this outcome, the authors should clearly note which outcome they are considering, and should provide some context about how this disordered is measured, both clinically and non-clinically.

More broadly, in the section on behavior, it should be noted that there is commonly overlap across types of behavioral problems. This overlap occurs both within a broad domain (“misconduct”, or “ attention problems”) as well as across domains (as when depressive symptoms are more common among individuals who also show conduct symptoms). In this light, investigations that allow for examination of hypothesized differences across domains in degree of association with lead exposure would seem to be key. In other words, a higher degree of certainty is provided by studies which look at Pb associations with both hypothesized and not-hypothesized outcomes, and which can demonstrate that exposure is related to A (as hypothesized) but not related to B (which was **not** hypothesized, but which can be measured in the same way). In our work in Yugoslavia, we did this, with different age-variations of the

CBCL at child age 3 and 4-5 years. In each case, using an instrument that assesses behavior in the same way (parent report) across a range of types (with a range of subscales for different content areas of behavior problems). Oddly, the ISA only cites the first study with preschoolers(Wasserman, GA; Staghezza-Jaramillo, B; Shrout, P; Popovac, D; Graziano, J. (1998). The effect of lead exposure on behavior problems in preschool children. Am J Public Health 88: 481-486. http://dx.doi.org/10.2105/AJPH.88.3.481) and does not refer to the more recent investigation with slightly older children at all (Wasserman GA, Liu X, Pine DS, Graziano JH.Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. Neuurotoxicol Teratol. 2001 Jan-Feb;23(1):13-21). There were 2 studies because the CBCL offered one instrument for the younger ages, and a somewhat different checklist for the older children.

Here is the abstract for the preschool study (1998): OBJECTIVES: Interpreting associations between lead exposure and child behavior problems is difficult because studies have not controlled for sociodemographic confounders or have used shed teeth to mark exposure. This study explored associations between blood lead and preschool behavior. METHODS: Children from a smelter town and a non-lead-exposed town in Yugoslavia were followed up prospectively from pregnancy through age 3. The Child Behavior Checklist was used to assess behavior problems in 379 3-year-olds, controlling for sociodemographic factors and difficult infant temperament. RESULTS: Multiple regression revealed the expected significant associations between checklist subscales and sociodemographic factors, which explained 7% to 18% of the variance on the subscales. Concurrent blood lead explained a significant 1% to 4% of the variance on the Destructive and Withdrawn subscales. Earlier difficult temperament explained an additional 2% to 5% of the checklist variance. Scores on the Destructive subscale were consistently associated with blood lead. As blood lead increased from 10 to 20 micrograms/dL, subscale scores increased by approximately 0.5 points. CONCLUSIONS: Lead/behavior associations are significant but small compared with the effects of social factors.

And here is the abstract for the study with 4-5 year olds: Maternal smoking during pregnancy elevates risk for later child behavior problems. Because prior studies considered only Western settings, where smoking cooccurs with social disadvantage, we examined this association in Yugoslavia, a different cultural setting. Mothers enrolled in pregnancy as the low-exposure group in a prospective study of lead exposure were interviewed about health, including smoking history. A total of 199 children were assessed on the Child Behavior Checklist (CBCL) at ages 4, 4 1/2, and 5 years. Average cumulative blood lead (BPb) was determined from serial samples taken biannually since delivery. Longitudinal analyses were derived from 191 children with available data on behavior and covariates. Smoking was unrelated to social adversity. Controlling for age, gender, birthweight, ethnicity, maternal education, and Home Observation for Measurement of the Environment (HOME) Acceptance, smoking was associated with worse scores on almost all subscales; BPb concentration was related to small increases in the Delinquency subscale. Daughters of smokers received significantly higher scores on Somatic Complaints compared to daughters of nonsmokers, consistent with other work relating biological factors and internalizing problems in young girls. Because the present smoking/child behavior associations persist after control for individual and social factors also related to behavior problems, possible biological mediators are considered.

To summarize, then, among 3-year olds, we found that, adjusting for sociodemographic features and infant temperament, concurrent blood lead explained a significant 1% to 4% of the variance on the Destructive and Withdrawn subscales (at this age, there is no subscale measuring attention problems, and the Destructive subscale maps most closely onto misconduct). With the version of the CBCL that does measure both attention and misconduct, at age 4-5, adjusting for sociodemographic features, childrearing, and in utero exposure to smoking, we reported significant associations between Pb exposure and misconduct (Delinquency) but not with Attention Problems, in the paper that was NOT cited in the ISA. Neither study, then, found support for a specific association with attention problems, although misconduct was related to exposure.

2. How adequately has evidence been integrated between toxicological and epidemiological studies, in particular the increased emphasis on toxicological findings most relevant to Pb-associated effects in humans

Overall, I think there is far more integration across the modes of scientific inquiry (epidemiology and toxicology). This makes interpretation much more accessible for the reader. Within the information presented on cognitive and behavioral endpoints, I think there are two places where more should be provided.

First, on 5-91 in the text at bottom of page. I think it is quite a leap to equate maternal self-esteem in humans with maternal stress in animals. In other areas of investigation, for example, maternal stress in animals has been used in models for maternal depression.

Second, on page 5-92 L 22, "overall FI rate" is designated "a hyperactive behavior". Do the authors mean "overactive"? Do they mean to reference the disorder of ADHD? Would a mention of impulsivity be more apt? So much of ADHD relates to issues of distractibility and impulsivity, rather than movement, that this is confusing. We need the dots to be connected here.

3. How well does the document integrate scientific evidence both within sections for specific endpoints and summary sections.

The authors have clearly expended effort to provide the cross-talk that this document needed, within and across endpoints. I think it reads better and more forcefully now.

4. Do conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and the populations examined (e.g., school-aged children, adolescents, adults with and without occupational exposure).

Overall, a fair and thorough presentation of the evidence.

5. Are inferences regarding the specific Pb exposure scenarios (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?

5-52 L 21-27. It's not clear if second half of this paragraph is referring back to the Lanphear pooled analysis or to the base of work reviewed in the 2006 document, or to something else.

Similarly, in the "most strongly indicated in children with……" sentence, it should probably be clarified that the differences in the exposure levels most commonly identified as promoting risk are related to the distributions of exposures in the populations studied, and not really to identifying which exposure is most risky.

Further substantive concerns:

5-63 Fig 5-3. In presenting this figure from its original source, considerable information was not carried over in the figure legend, making this impossible to understand. Specifically, that the 3 lines reflect CI's, what is the meaning of "A" and "B", and what units are presented (both exposure and IQ are presented with negative values, no units indicated). Figure 5-12 (on page 5-111) does a better job at explaining what is being shown.

5-66 L1 "MDI scores are….[substitute for " not necessarily" instead "only modestly"] correlated with IQ scores". It's not that this association appears sometimes, it is that it is of small magnitude. I think this is an important distinction, as it speaks to the underlying construct, not just to variability across investigations.

5-213-216 Overall, I think the discussion of public health significance adds considerably to the weight of the evidence presented. On the other hand, there are still problems with the discussion that relates to increasing the proportions of individuals in the clinical range for IQ. This relates back also to the figure presented on p 2-55. It's noted on P 214 that these projections are based "on purely statistical grounds" but I don't think the distinction between an illustrative model and actual data is really highlighted. And these models are still based on the assumption that the impact of Pb is the same across all levels of ability, which is something we don't know, and which should be explicitly indicated. Here in chapter 5 (and again in chapter 2) it should be clearly stated, if this figure is to be provided, that it is a model, for illustration only, and it assumes that the impact of exposure is the same at every point on the ability curve (for which there is little, or no, evidence).

The evidence that is provided, as in particular vulnerabilities of children at low SES, and the possibility of earlier, accumulating deficits with some groups of children, supports the determination of public health significance

Smaller edits:

5-60 L 24. In which one study …[at a time]… was successively excluded" or something similar, for clarity

5-72 L 8 "because several tests…[and their underlying functions]….are interrelated". It's more important that the <u>constructs</u> interrelate, rather than that the measures *interrelate*

5-77 L 1 and 3. Words missing: "Rochester cohort [at] age 5 years" and "same tests [of] executive function"

5-78 L 21. Word missing "performance [on] a color-word"
5-79 L 17 Should read "blood Pb level, the decrease[s] in…"

5-84 L 9 Maybe not 2 "demonstrate"s in same line?

5-91 Table 5-7. This table is a bit telegraphic. Hard to see what is being shown. At least define NS, OS, and PS.
L8 Whose "ability to cope" are we talking about? Mom's? offspring's?

5-104 L 13. I don't know if it was defined elsewhere, but this is a long chapter, and NAS should be defined here, or redefined here, when it is discussed.

5-131 L28 What is meant by indirect effects?
L 34 missing word. "out [of] the range of…"

5-136 L 8, More proximal to this discussion, suggest writing out what is the CLS cohort?

5-137 L 15 "may [lie] on the"

5-141 L4 "investigation[s]"

5-144 L9. I think these are meant to be "disorders" rather than "symptoms"`

Chapter 6- Potentially at-risk populations

Charge questions:

1. … the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

2. … whether the designation of some factors as having limited evidence adequately reflects the knowledge base considered and strength of evidence available.

I think the evidence base is presented in a full fair manner. For some individual factors, even within a single outcome area, there are inconsistencies in the degree to which this factor relates to increased vulnerability to Pb exposure across studies. For example, on page 6-20, first paragraph, some studies find increased risk for males (as in frontal lobe grey matter loss in Brubaker and greater cognitive deficits in a Polish cohort), while others (as in Port Pirie) report poorer cognitive scores in females. These inconsistencies are mentioned as a reason for further research. Maybe there isn't any better way to

integrate these, but the fact that there are inconsistencies also speaks to the certainty with which we weight these findings, and this needs to be made more clear.

Overall, the discussion of the dynamic nature of some of these associations (the declining race differences in vulnerability in the US, for example) is informative.

6-34 L 4. Again, there is an equation suggested between maternal stress in animals and lower maternal self-esteem in humans (point also made on 5-91), that I think needs to be more fully considered.